KU LEUVEN

FACULTEIT GENEESKUNDE

FACULTY OF MEDICINE

LOGOPEDISCHE EN AUDIOLOGISCHE WETENSCHAPPEN
HERESTRAAT 49/721
3000 LEUVEN

Detecting hidden hearing loss using Auditory Steady State and Brainstem Responses

Yalenka Devrieze en Klara Schevenels

Verhandeling aangeboden tot het behalen van de graad van
Master in de Logopedische en Audiologische Wetenschappen

Promotor: Professor Dr. Francart Tom
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Introduction Noise overexposure can damage the auditory system, without affecting the hearing thresholds, which is called 'hidden hearing loss' (HHL). Because the traditional assessment of noise induced hearing loss focuses on these thresholds, a great deal of HHL is not observed in the clinical practice. Since HHL selectively damages high-threshold auditory nerve (AN) fibers, supra-threshold short-latency measurements like the ABR and the ASSR are more sensitive to reveal HHL.

Methods The AN of 13 persons, who were given a certain noise exposure score based on a self made hearing questionnaire, was in this study evaluated with short-latency ABRs and ASSRs at 50 dB A/nHL. The measurements were done to different stimuli (ABR: click, 4kHz toneburst, CE-chirp, 4kHz narrowband CE-chirp and ASSR: sweep of modulation frequencies of 35-300Hz and 40Hz and 275Hz amplitude modulated noise) and electrode configurations (two mastoid electrodes and one in-ear TIPtrode). Furthermore, because wave-I of the ABR is rather hard to detect, it was tried to find an ASSR correlate for this parameter in order to have a more robust diagnostic test for HHL.

Results No significant relations were demonstrated between the ABR parameters and the noise exposure scores. For the ASSR, there was found a significant negative correlation between the responses to the 40Hz amplitude modulated noise and the noise exposure scores, and smaller responses to the noise sweep in the range 150-250Hz were found for the subjects with a higher noise exposure score as measured with the TIPtrode. Due to a possible lower sensation level of the applied stimuli for subjects with higher noise exposure scores, these results should be interpreted with caution. Between the ABR and ASSR parameters, no significant correlations that met our expectations were found.

Conclusion Further research to detect HHL using the ASSR and the ABR is needed with more subjects.

Words of thanks

It took us two years of blood, sweat and tears to complete this thesis successfully. Through this process, a lot of persons have supported us. Therefore, we would like say special thanks to these persons.

First of all, we would like to thank our promotor, Professor Dr. Tom Francart, for his endless patience, everlasting willingness to answer our questions and for his precision, clear-sightedness and competence.

Professor Dr. Jan Wouters, thank you for educating us in the field of audiology and for being our copromotor.

Subsequently, we are very grateful for the support of the department expORL when we experienced difficulties during both measurement phases.

Importantly, we show special appreciation for all our friends who wanted to participate in this study and for all the effort they have made during and even after the measurements. Without them, this study would not have become what it is today.

Furthermore, we would like to thank our parents and stepparents for all the chances they have given to us for personal growth. Without them, we would never have been where we are now.

Thanks to our grandparents and our sisters Ylonka and Evelien for the loving support in difficult times and for their soothing words whenever we needed them.

Thomas and Bram, our boyfriends, are thanked for their listening ear, their unconditional support and for always being there when we needed someone to hear our frustration.

Next, we want to express gratitude towards all of our friends for giving us courage during these two years. Special thanks goes to our fellow students Judith and Inès, who have become special friends after four years of studying together. We know we can rely on you for all of our problems.

Additionally, we say thank you to Hendrik, Yorick, Stijn and Evelien for proofreading our thesis and helping us with the layout.

We also want to thank our readers, for their interest in our research.

Last but not least, we would like to thank each other for the support during and next to the many hours of working together day and night, seven days a week, 24 hours a day. The making of this thesis has intensively strengthened our friendship.

II

Contents

List of abbreviations

ABR: auditory brainstem response(s)

AEP: auditory evoked potential(s)

AM: amplitude modulated

AN: auditory nerve

APEX: application for psycho-electrical experiments

ASSR: auditory steady state response(s)

BM: basilar membrane

CAP: compound action potential

CE-chirp: Claus Elberling chirp

CL: contralateral

dB nHL: dB normal hearing level

dB p-peSPL: dB peak to peak equivalent SPL

dB SL: dB sensation level

dB SPL: decibel sound pressure level

DPOAE: distortion product oto-acoustic emissions

DTT: Digit Triplet Test

EEG: electroencephalogram

ER-3A: Etymotic research – 3A earphone

FFT: Fast Fourier Transform

HC: hair cells

HHL: hidden hearing loss

HL: hearing loss

HQ: hearing questionnaire

i.a.: inter alia

IE: in ear

IHC: inner hair cell(s)

IL: ipsilateral

NH: normal-hearing

NIHL: noise-induced hearing loss

OHC: outer hair cell(s)

peRETSPL: peak-to-peak equivalent reference equivalent threshold sound pressure level

SAM: sinusoidal amplitude modulated

SNR: signal-to-noise ratio

SOC: superior olivary complex

SR: spontaneous rate

SRT: speech reception threshold

TM: tympanic membrane

TTS: temporary threshold shift(s)

General introduction

Noise-induced hearing loss (NIHL) is an important health problem, considering noise is nowadays inseparable of many people's way of living. On top, this kind of hearing damage does not have to be painful (Kujawa & Liberman, 2009). Recently, it has been discovered that an overexposure to noise can cause damage to the auditory system, without even affecting the thresholds of hearing. This is called 'hidden hearing loss' (HHL). Since the traditional assessment of NIHL focuses on these thresholds, a great deal of this type of hearing loss is not observed in the daily clinical practice.

Since a decade, with the upswing of technology in small devices, the access to personal music players has considerably increased. Also, more and younger adolescents and young adults attend festivals, concerts, discotheques and other activities where sound levels exceed the tolerance of our hearing system after some time. For all this, it is possible that many adolescents and young adults suffer from HHL without knowing. This kind of hearing loss (HL) has been shown to cause an immediate loss of inner hair cell synapses and nerve terminals of low spontaneous rate (SR) auditory nerve (AN) fibers, despite complete recovery of cochlear sensory cells after temporary threshold shifts (TTS). This specific loss eventually causes primary degeneration of the AN and this has several dramatic consequences for our hearing ability (Furman et al., 2013; Kujawa & Liberman, 2009). People with HHL have i.a. difficulties with understanding speech in noisy environments. Tinnitus, hyperacusis and other perceptual anomalies have also been linked to this kind of HL (Kujawa & Liberman, 2009).

Auditory steady state responses (ASSR) and auditory brainstem responses (ABR) are two objective methods to evaluate how the auditory brain responds to a variety of sounds. The brain activity is assessed by means of an electroencephalogram (EEG) and an EEG in response to auditory signals is called 'auditory evoked potentials' (AEP). ASSR and ABR are two different subdivisions of these potentials. These methods evaluate the different structures on the auditory pathway, depending on the applied stimulus parameters. The main difference between these two methods is the analysis procedure: ABRs are assessed in the time domain and ASSRs in the frequency domain. Furthermore, these methods are shown to be able to detect HHL in mice and guinea pigs when short-latency responses at supra-threshold levels are assessed (Furman et al., 2013; Hickox & Liberman, 2014; Kujawa & Liberman, 2009; Shaheen et al., 2012). Therefore, in this study, these supra-threshold measures of auditory function are used to evaluate the auditory system of young adults with different modes of life concerning noise

exposure and behaviour towards noise. In this way, we have tried to demonstrate HHL in a possibly affected population.

Before explaining the practical part of our research, in chapter one, we will review the existing literature concerning HHL. A significant amount of research about how HHL can be detected in animals, by inducing it using a specific neuropathic stimulus followed by applying invasive methods, exists. Furthermore, it is described how this kind of HL gives rise to harmful long-term consequences. In humans, the procedure to detect HHL used in animals is not ethically justified. First, one cannot expose humans to noise for research purposes and second, invasive methods cannot be applied to detect this pathological condition. To by-pass the first obstacle, a hearing questionnaire (HQ) is frequently used in literature to assess the subject's history of noise exposure. In chapter two, the importance of recreational noise exposure in the development of HHL and a few studies who administered HQs are described. In the third chapter, the objective non-invasive alternative methods with which HHL is tried to detect in humans in this study are described and in chapter four the research questions of this study are presented. Subsequently, the two following chapters give extensive information about the used methods and the obtained results of our study. In chapter seven, the results are interpreted, discussed and compared to the literature and verified against our research questions. This is followed by a description of the practical and theoretical implications, limitations and suggestions for follow-up studies. To conclude, a summary of the main points of our research is given.

Chapter 1: Hidden hearing loss

1.1 Introduction

Overexposure to noise can cause HL, despite complete recovery of thresholds. Yet, threshold measurements still function as the gold standard for the assessment of hearing sensitivity. When the inner ear is overexposed to noise, thresholds will shift to higher values. These thresholds usually recover to their normal values after a couple of hours. This phenomenon is called 'temporary threshold shift (TTS)'. The absence of delayed threshold shifts after noise exposure was formerly the proof that noise caused no long-term permanent damage to our hearing ability and thus the TTS has been harmless (Humes et al., 2005). However, it has been questioned whether there really are no consequences to temporary NIHL and indeed, noise has recently been linked to several dramatic long known perceptual anomalies like tinnitus

(the perception of phantom sounds) and hyperacusis (hypersensitivity to sound) without threshold elevation (Hickox & Liberman, 2014; Schaette & McAlpine, 2011). More common and frequent hearing problems like decreased speech discrimination in noisy environments can also be the direct consequence of overexposure to noise (Kujawa & Liberman, 2009).

1.2 Appearance and progress

1.2.1 In experimental animals

Recently, several researchers have demonstrated the presence of HHL in mice and guinea pigs. Both Kujawa & Liberman (2009) and Shaheen et al. (2012) demonstrated HHL in mice in the following manner. Mice were exposed for a few hours to a high-intensity octave band of noise (8-16 kHz) that especially had been designed to produce cochlear neuropathy in the basal half of the cochlea without permanent threshold shift. All objective threshold measurements initially shifted to higher values, but fully recovered two weeks post exposure, reflecting TTS. In contrast, all supra-threshold objective measurements of the AN fibers (the ABR wave-I amplitude, the compound action potential (CAP) amplitude and the ASSR amplitude and phase to high modulation frequencies around 1 kHz) did only recover to 40% of pre-exposure amplitudes at 32 kHz, suggesting neuronal loss. The threshold and supra-threshold findings are presented in figure 1.

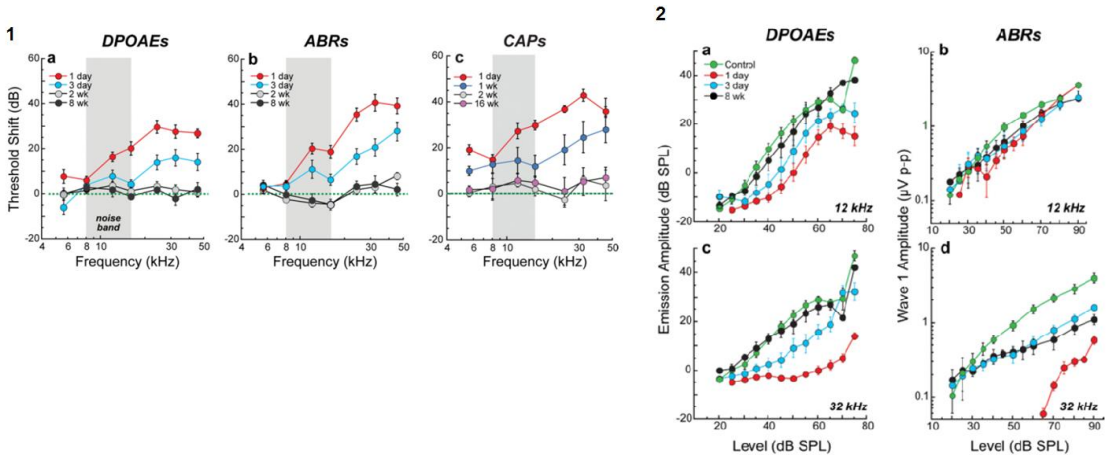

Figure 1. *Threshold and supra-threshold AEP measurements.* Part 1: DPOAE, ABR and CAP threshold shifts, after being exposed to a 100 dB SPL noiseband (grey shade) for 2 hours, have recovered 2 weeks post exposure. Part 2: supra-threshold neural responses at high frequencies (32 kHz) are permanently affected, although DPOAE fully recover, suggesting normal cochlear hair cells. Adopted from Kujawa & Liberman (2009).

Additionally, distortion product oto-acoustic emissions (DPOAEs, measurement of the outer hair cells (OHC)) and confocal imaging of the sensory epithelium in the cochlea demonstrated no loss or permanent damage to hair cells (HC) for at least one year. But, confocal imaging did show rapid, extensive and irreversible loss of synapses between inner hair cells (IHC) and coch-

lear nerve fibers and extensive degeneration of cochlear nerve terminals throughout the basal part of the cochlea (>4 kHz, 50% at 32 kHz), within 24 hours post exposure. This finding is in agreement with the decrement of supra-threshold measurements at high frequencies. Because of the degeneration of cochlear nerve terminals, cochlear neurons theirselves also progressively degenerated, but extremely slowly (over many months to even years). Two years post exposure, ganglion cell counts in the 32 kHz region had decreased by 50%. These results prove that the cochlear neural degeneration caused by acoustic overexposure is a primary event and not secondary due to the loss of HC. These results also confirm the finding that threshold measurements (of any kind) fail to provide evidence for neurodegeneration and this is why this kind of HL is called '*hidden* hearing loss'. The cochlear nerve degeneration is put in motion as early as 24 hours post exposure, when nerve terminals are lost, and is irreversible.

The fact that the found decrease in AEP parameters in all these studies was minimal at near-threshold levels at which the low-SR fibers do not fire, and was maximal at moderate intensity levels at which the low-SR fibers do fire (Shaheen et al., 2012) and the fact that approximately 40% of the IHC synapses could be irreversibly lost without any influence on threshold measurements while the cochlear nerve consists in 40% of low-SR fibers (Furman et al., 2013), suggests that this noise-induced cochlear neuropathy is selective for low-SR nerve fibers. This selective loss provides a natural explanation for the recovery of thresholds but not the supra-threshold amplitudes, as the low-threshold fibers remain undamaged. The underlying physiology of the mechanisms giving rise to HHL, is described in detail in appendix A.

Shaheen et al. (2012) have additionally provided suggestions for methods to detect HHL in humans. They argued that, because ABR amplitudes are more variable in humans than in mice, they cannot be used for a reliable diagnosis of HHL. The ASSR in response to sinusoidal amplitude modulated (SAM) tones, in contrast, provides a higher signal-to-noise ratio (SNR) than ABR and phase consistency (that can be derived from the ASSR) is less affected by intersubject variability. Therefore, they compared ASSR and ABR in the mice with noise induced primary nerve degeneration. The decreases in ASSR amplitude and phase at 32 kHz were found to be more robust than the decrease in ABR wave-I amplitude at 32 kHz in mice, for the same acquisition time. Furthermore, they demonstrated that phase consistency of the ASSR will probably be the most robust measurement of HHL in humans by comparing ABR and ASSR after adding amplitude variability to simulate the situation in humans.

1.2.2 In humans

Stamper & Johnson (2014) tried to demonstrate the previously described HHL in humans. Since humans cannot be exposed to neuropathic noise on purpose, a HQ served as an assessment of the normal-hearing (NH) subjects' noise exposure history. In the self-report HQ developed by Megerson (2010), it is assessed how frequent and how long subjects were exposed to nine high noise situations (for details, see the appendix of their study). Their noise exposure background was subsequently calculated based on the annual amount of noise exposure in $L_{Aeq8760h}$. 'L' represents the sound pressure level in dB, 'A' represents an A-weighted frequency response, 'eq' represents a 3-dB exchange rate for calculation of the time-level relationship and '8760h' represents the number of hours in one year. The researchers found that the main cause of higher noise exposure background was music listening behaviour.

In the light of the previously described studies, they wanted to assess whether this noise exposure had affected DPOAE and ABR amplitudes in response to 100 µs clicks and 2 ms 4 kHz Blackman windowed tonebursts at intensities decreasing from 90 dB nHL to -10 dB nHL. Both an ipsilateral (IL) mastoid electrode and an IL tympanic membrane (TM) electrode configuration were used. A systematic and significant trend of smaller ABR wave-I amplitudes with greater history of noise exposure was found, but only at high stimulation levels (≥70 dB nHL) and only in the mastoid electrode configuration. At stimulation levels ≤60 dB nHL this relation attenuated and disappeared. Using the TM electrode, similar relations were found but did not reach statistical significance due to a larger intersubject variability associated with the recording site. Supra-threshold DPOAEs and ABR wave-V amplitudes were not significantly related to noise exposure background. In general, these findings are in agreement with the experimental animal studies.

1.3 Sequelae

1.3.1 Hearing in noisy environments

It is clear that the NIHL described in mice, and the following neurodegeneration, is assumed to occur in humans too. Since the loss is selective for low-SR fibers that connect to the IHC, and the cochlear nerve consist in 95% of IHC sensory fibers (Spoendlin, 1972), the degeneration must have long-term consequences for our hearing ability. These low-SR fibers (with high thresholds of activation) are important for increasing the dynamic range of the auditory periphery up to 120 dB. Additionally, high threshold fibers are more resistant to masking by con-

tinuous background noise (Costalupes et al., 1984) and thus very important for hearing in noisy environments (Furman et al., 2013). The loss of low-SR fibers therefore impedes good processing of stimuli with a low SNR (e.g. speech in noise). Thus, patients with HHL can have increased tone and speech detection thresholds in high-intensity background noise (Weisz et al., 2006).

1.3.2 Tinnitus and hyperacusis

Peripheral damage also influences central processing and this phenomenon could give rise to tinnitus and/or hyperacusis, that are often comorbid because their pathophysiologic mechanisms overlap (Schecklmann et al., 2014). It has been demonstrated in humans with peripheral damage that these phenomena are indicators of an abnormal growth in spontaneous (tinnitus) and stimulus-driven (hyperacusis) activity of the central auditory system (for review, see Eggermont, 2013). However, many tinnitus patients present with a normal audiogram (e.g. Coelho et al., 2007; Schmuziger et al., 2006). In the previous part, it has been described that NH thresholds do not necessarily indicate the absence of cochlear damage. Overexposure can cause widespread cochlear nerve degeneration without permanent threshold shifts.

Schaette & McAlpine (2011) reported direct physiological evidence for HHL in human subjects with tinnitus and a normal audiogram. They hypothesized that deafferentiation of a large part of the AN fibers, which occurs in HHL, could trigger the development of tinnitus in the central auditory stations via homeostatic mechanisms that normalize levels of activity in the central auditory system and proved this in an established computational model (for details, see Schaette & McAlpine, 2011). To stabilize mean neuronal activity in the central system, homeostatic plasticity increases the excitability and decreases the inhibitory gain in neurons to restore the average activity to normal. Because the neurons consequently become more excitable, they also exhibit more spontaneous activity which leads to hyperactivity. This could trigger the generation of tinnitus. In their subjects with tinnitus and a normal audiogram, the HHL was objectively seen as reduced supra-threshold ABR wave-I amplitudes. In contrast, ABR wave-V amplitudes, generated at the level of the midbrain, were normal. This was expected from previously described studies. With the introduction of this homeostatic mechanism, they thus provided an explanation for the unchanged wave-V amplitudes in HHL, while the wave-I amplitudes are reduced. HHL can therefore be detected in ABR measurements as an enhancement of the wave-V/I ratio. Additionally, they demonstrated deafferentiation specifically for the low-SR fibers through a reduction in AN output at higher sound levels. Besides, Hickox & Liberman

(2014) suggested in mice with HHL a relation between AN degeneration and central hyperactivity that could underlie hyperacusis.

Chapter 2: The impact of recreational noise exposure

Overexposure to recreational noise thus can result in HHL and this in turn can result in NIHL, which is visible in the audiogram as a dip at and around 4 kHz (Attias et al., 2014). In contrast to HHL, NIHL is considered as an important health problem because of the visibility in the audiogram and because noise is interwoven in many people's way of living. NIHL in young adults and adolescents has increased over the last years, mostly due to loud music exposure. Young people expose themselves to potentially damaging loud sounds during leisure activities, e.g. going to discotheques and listening to portable audio players (Axelsson & Jerson, 1985; Chung et al, 2005; Dalton et al, 2001; Sadhra et al, 2002). Therefore, it is possible more and more young people suffer from HHL, without knowing.

Many studies have demonstrated the prevalence and characteristics of recreational noise exposure in adolescents and young adults. In different studies, the subjects' noise exposure history is assessed in different ways. Most studies obtained their results by comparing HQs with audiometric measurements and handle two important sources of noise exposure: discotheque/party/festival attendance and/or listening to personal audio players. Vogel et al. (2010) demonstrated that frequent discotheque visitors (one fourth of all visitors) took measures against hearing damage the least (e.g. less often taking noise breaks and more often standing within 2 meters of the loudspeakers) and that in general very little hearing protection was used. Judging the number of visits of adolescents may therefore be a first and quick screener to see if an adolescent poses a risk for HL due to discotheque attendance. They also indicated that environmental interventions may be most effective to prevent NIHL in adolescents attending discotheques (e.g. ear protection devices, keeping a certain distance clear around the loudspeakers and provide locations with low-volume music at noisy events). Vogel et al. (2010) stated that discotheque attendance constitutes a greater risk of HL compared to extended exposure to personal audio player music.

However, a study in Health Canada's laboratory demonstrated that, at the maximum volume of the personal audio players, the output can range from 101 to 107 dB A (Keith et al, 2008). Keith et al (2011) also reported in their study that 3% to 9% of subjects used their listening devices at levels exceeding the safety limit of 85 dB A over eight hours (THINKSAFE, 2013).

Another danger is that extended periods of listening time are possible due to the advanced technology (easier portability and longer battery life) (Hodgetts et al, 2007; Keith et al, 2011). Furthermore, Feder et al. (2013) demonstrated that subjects who used their device for five years or more had higher hearing thresholds for high frequency pure tone audiometry (averaged thresholds over 4 and 8 kHz), compared to subjects who reported using their device for less than a year. Also, significantly higher measured sounds pressure levels were demonstrated in subjects who reported listening to their device for six hours per week or more, compared to those who reported listening to their device for less than four hours per week. Thus, because of all this, extended listening to portable audio players can also be damaging for the hearing system. Besides discotheque attendance and listening to personal audio players, subjects also engaged in many other leisure noise sources. For example, Tung & Chao (2013) assessed discotheque attendance, earphone-use habit as well as other leisure noise sources in a HQ. There was found a significant difference in the total dose of recreational noise exposure in a year between subjects with high noise exposure and subjects with low noise exposure, but the pure tone audiometry test results theirselves did not show any significant difference. However, as mentioned in chapter one, this test is insensitive to detect HHL and thus does not exclude this possibility. Tung & Chao (2013) attributed this to the fact that NIHL is caused by long-term noise exposure and thus the dose of noise had not yet been harmful enough. They do suggest that such short time exposure to recreational noise causes TTS.

Many studies have also demonstrated the consequences of recreational noise exposure in adolescents and young adults. The most direct consequence is demonstrated to be measurable HL on the audiogram. But, also other symptoms, such as tinnitus which can even occur without measurable changes in hearing thresholds (Schaette & McAlpine, 2011) and TTS, are frequently occurring phenomena in young people after recreational noise exposure. Symptoms of TTS were reported in the study of Feder et al. (2013) by 33% to 50% of the subjects, whereas tinnitus was reported by 25% of the subjects, which seems comparable to other research study findings. All these findings clearly demonstrate the risk noise exposure poses to our hearing system. Interestingly, the prevalence of noise-induced symptoms is in contradiction to the low preventive use of hearing protection. Since TTS is a frequent self-reported consequence of recreational noise overexposure and this phenomenon is thought to cause HHL, HHL can be seen as a precursor of NIHL. Therefore, one could prevent NIHL by the detection of HHL.

Chapter 3: Objective methods of hearing

3.1 Introduction

Since temporary NIHL selectively damages AN fibers that respond to high-level sounds, supra-threshold measurements are more sensitive to reveal auditory damage than threshold measurements. In this chapter, an overview of the principles of the ABR and ASSR, which are demonstrated to be objective methods to assess HHL in chapter one, is given.

When we provide a stimulus to the ear, electrical brain activity (EEG) can be measured in response to that stimulus. An EEG in response to auditory signals is called AEP. Depending on how long it takes for a response to be measured (latency), the responses are divided into different categories: early responses (0-10 ms), middle latency responses (10-60 ms) and late responses (50-500 ms). The waveform of these responses is shown in figure 2. The responses with the shortest latencies are generated by the inner ear and the AN. Unique response patterns a few ms later reflect activity within the auditory brainstem. After that, response patterns due to activity in higher auditory parts of the brain, such as the cerebral cortex, occur (Hall, 1992).

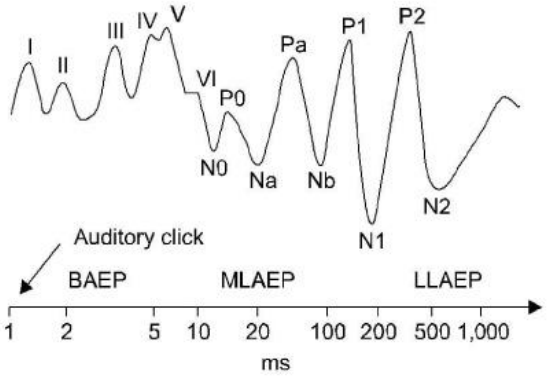

Figure 2. *Early (BAEP), middle (MLAEP) and late (LLAEP) latency auditory evoked potentials in response to the click. Adopted from http://synapse.koreamed.org/DOIx.php?id=10.4097/kjae.2007.52.3.253.*

In literature, different kinds of AEP exist. When a single brief stimulus or series of brief stimuli at low repetition rates are presented to the subject, auditory transient responses are evoked. These responses are evoked by stimulus changes, while sustained responses last through the duration of the stimulus. Both transient and sustained responses are evoked by repetitively changing stimuli, but when these changes are periodic, these responses are called ASSRs (Picton et al., 2003). Transient responses produced by auditory structures up to the brainstem are often called ABRs. In what follows, we will use the term ABR in stead of auditory transient responses, as is commonly done in literature.

3.2 Recording and processing of the responses

In this section, it will be described how the AEP can be recorded from the human scalp and which processing techniques are necessary to render the responses measurable. First, an auditory stimulus must be presented to the subject's ear. Previous to stimulus presentation, a process of digital stimulus generation must occur, followed by digital-to-analog conversion. Before the recorded EEG signal will enter the computer, the reverse operation (analog-to-digital conversion) will occur. To record the AEPs, electrodes are placed on the subjects' scalp. The precise location of the electrodes on the scalp can differ (for a review of studies evaluating different configurations, see 3.3.1.2), but there are in each electrode configuration several active electrodes, a reference electrode and a ground electrode (Hall, 1992).

When the stimulus is provided to the subject, only a small amount of the EEG is caused by the stimulus itself and this is called the *signal*. All of the remaining activity is called *noise*. This noise can originate from the subject itself, or from another source nearby. Examples of noise caused by the person itself are muscle activity due to blinking and swallowing and other brain activity that is not related to the stimulus. Other sources include electromagnetical activity originating from electronic devices and noise induced by the measurement itself. The amplitude of the noise (in the order of 10 to 20 μV) is far greater than the amplitude of the signal (a few μV or even nV). In order to be able to register the specific response to the auditory stimulus, the SNR must be of sufficient size. In order to realise this, four steps are basically applied to the recorded activity: (1) amplifying and common mode rejection, (2) bandpass filtering, (3) artefact rejection and (4) averaging (Lamoré, 2011; Lamoré & Kapteijn, 2008). These signal processing techniques are described briefly below.

First, to magnify the AEPs generated by the cochlea, the vestibulocochlear (VIIIth) nerve or the brain, an amplifier is a crucial component of an evoked response system. The amplifier also applies common mode rejection. The recording electrodes are placed at different locations on the scalp, but will presumably detect the same amount of electrical interference in the region of the scalp. Common mode rejection is referred to as a subtraction process because the activity that is common at each electrode is considered as noise and eliminated (Hall, 1992). Second, bandpass filters are indispensable to detect a signal in the presence of background electrical noise. They pass energy at certain frequencies and reject electrical energy at other frequencies and since the noise and the AEP have different frequency contents, this noise can be filtered out of the raw electrical activity detected by the electrodes (Hall, 1992). Third, artefact

rejection is necessary to eliminate subject-related high noise levels from the EEG due to e.g. swallowing and movements and is based on an amplitude measurement of the response signal (Picton et al., 2003). In this way, only the artifact-free EEG is passed on to the averaging process (Hall, 1992), which is the fourth signal processing technique to further improve the SNR. Assuming the response signal is stable in each recording and the noise is random, the averaging operation will cause the amplitude of the noise to decrease while the amplitude of the signal is maintained (Picton et al., 2003). The filtering, artefact rejection and averaging take place after digitalisation of the signal. In the following section, further analysis of the AEPs will be described for the ABRs and the ASSRs separately.

3.3 Response analysis

3.3.1 Analysis of the ABR

The EEG that is recorded must be converted back to a digital signal in order to be able to represent the EEG on the computer. The EEG signal is then digitally saved in small elements called epochs, usually with a length of one period. A 'sweep' is composed of several consecutive epochs (John & Picton, 2000) and an average of several 'sweeps' is calculated to represent the response in the time domain, which is required for the analysis (John & Purcell, 2008). The ABR is represented by a typical wave pattern containing seven waves of which wave I, III and V are best detectable. These waves are characterized by their latency (differences) and amplitude. The detection and interpretation of these waves occurs visually and is therefore subjective.

3.3.1.1 The waveform pattern

The different waves are evoked by different stages on the auditory pathway: wave-I represents the cochlear nerve and wave-V represents the brainstem. More specific, wave-I is the far field equivalent of the CAP, generated in the distal portion of the VIIIth nerve, leaving the cochlea and entering the internal auditory canal. For wave-II, the generator is the proximal portion (brainstem portion) of the VIIIth nerve. Wave-I and wave-II are thus action potentials generated by the AN. The generator of wave-III is the trapezoid body of the cochlear nucleus and the generator of wave-IV is the superior olivary complex (SOC). Wave-V is evoked by the transition of the lateral lemniscus into the inferior colliculus. Later waves have multiple generators and may reflect postsynaptic activity in major auditory brainstem centers (Hall, 1992). All generators are summarized in figure 3.

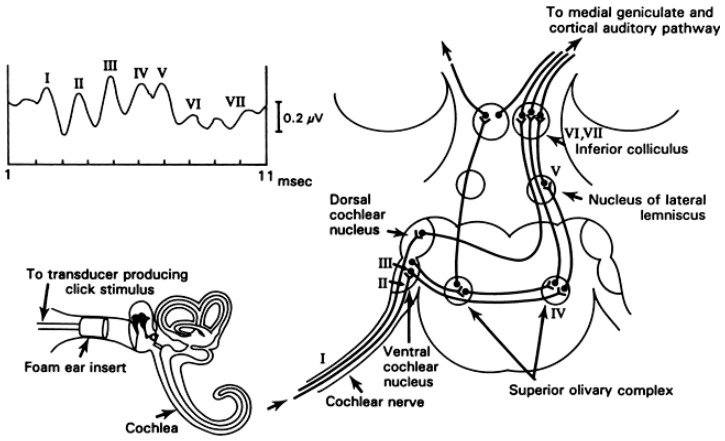

Figure 3. *The anatomical generators of the seven ABR waves*. *Adopted from http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v03/030453r00.HTM.*

3.3.1.2 Measuring wave-I

Even when wave-V is present a clear wave-I is not always discernible in ABR, especially at low intensity levels. The identification of wave-I and the interpeak interval I-V, however, is important for the identification of neurological and audiological dysfunction (e.g. Hecox & Galambos, 1974). Also in our study wave-I plays a particularly important role, as we expect lower amplitudes in subjects who have been frequently exposed to recreational and/or occupational sounds (see 1.2.2). Although the ABR is conventionally measured using far field electrodes in a vertex-mastoid configuration, several studies have succeeded to increase the amplitude and clarity of wave-I, without sacrifying wave-V amplitude or clarity, using ear canal electrode configurations (Bauch & Olsen, 1990; Beattie & Lipp, 1990; Stamper & Johnson, 2014; Yanz & Dodds, 1985, Zhang, 2010). However, in the study of Yanz & Dodds (1985), the significant difference between both configurations disappeared at intensities at and below 60 dB nHL. Furthermore, the ear canal electrodes do not have the same effect on wave-V amplitude. For this wave, the electrode configuration with the mastoid electrode seems to be more advantageous (Bauch & Olsen, 1990; Zhang, 2010). These reports indicate the advantage of electrode placement closer to the neural origin of the response. For wave-I, this means the recording electrode should be placed as close as possible to the AN, while for wave-V, the mastoid is a better choice due to its proximity to the auditory brainstem (Yanz & Dodds, 1985).

An example of an ear canal electrode is the TIPtrode used in the study of Bauch & Olsen (1990). The TIPtrode is a foam plug wrapped in a thin layer of gold foil that can easily be inserted into the ear canal. This plug is connected to an Etymotic research-3A (ER-3A) transducer with silicon tubing and therefore has two functions: stimulus presentation and response recording. As described above, the main advantage of the TIPtrode is that, due to the amplitude

enhancement, wave-I itself (but also the interpeak intervals I-III and I-V) can be obtained more accurately in patients. Second, the foam material has a comfortable fit in the subjects' ear canal. However, TIPtrodes are disposables and therefore quite expensive when used frequently. Second, the test time can increase due to a higher preparation time, especially when there is a lot of cerumen in the meatus (Bauch & Olsen, 1990). The ear canal skin needs therefore to be thoroughly cleaned and scratched with an abrasive gel to lower impedance, and this can cause irritation. Third, the gold foil is easily damaged by squeezing the plug to insert it (Zhang, 2010). Finally, Stamper & Johnson reported a larger intersubject variability associated with the ear canal recording site. However, Yanz & Dodds (1985) reported no difference in amplitude variability between the ear canal and mastoid electrodes.

3.3.2 Analysis of the ASSR

Once again, several consecutive epochs of the digitalised EEG, this time usually with a length of 1.024 s, are assembled into a 'sweep' (John & Picton, 2000) and an average of several 'sweeps' is calculated to represent the response in the time domain (John & Purcell, 2008). However, ASSRs are recorded by frequency based analysis procedures. Because these responses are typically locked to the stimulus modulation frequency/rate, transferring these responses to the frequency domain yields a peak at the modulation frequency and at integer multiples of this frequency (harmonics), which represents the periodicity of the response. The strength of these ASSR components represents the sensitivity of the auditory system to this modulation frequency. In the stimulus there is no energy at the modulating frequency, but this peak appears due to nonlinearities in the auditory system (Purcell et al., 2004).

The average EEG 'sweep' to a stimulus with a fixed modulation frequency (see 3.4.2.1) is digitally transformed from the time domain to the frequency domain by the fast Fourier transform (FFT) (Cooley & Tukey, 1965). The FFT calculates amplitudes and phases for a range of frequencies (0 to half of the sample frequency) based on the original amplitude-time waveform multiplied with a sine or cosine with a frequency equal to the modulation frequency. The spectral resolution of this conversion is the reciprocal of the duration of the 'sweep' that is fed to the FFT algorithm and determined by the sample frequency. The duration of the 'sweep' is in turn determined by the speed and memory of the computer, together with the resolution required for response discrimination (Picton et al., 2003). The sampling rate is the precision in the time domain with which the response is converted from analog to digital (John & Purcell, 2008). The average EEG 'sweep' to a stimulus with a sweeping modulation frequency (see 3.4.2.2), in contrast, is transformed to the frequency domain by the Fourier analyzer. In sum-

mary, the Fourier analyzer calculates the amplitude and phase of the recorded activity having the same fundamental frequencies as the sweeping modulation frequency of the stimulus by multiplying the average EEG with a (co)sinusoidal sweep of these modulation frequencies (Stapells et al., 1984). Thus, the analyzer has orthogonal reference sinusoids matching the instantaneous frequency of the stimulus (Regan, 1989). The principle of this analyzer is further discussed in Purcell et al. (2004), Regan (1989) and Stapells et al., (1984).

After these Fourier transformations, statistics are used to detect the significance of this peak at the modulation frequency of the stimulus (the ASSR) relative to the ambient EEG noise. The advantage of using statistical tests is that it makes sure that the ASSR method is objective. These tests can both be applied on the amplitudes and phases of the ASSR (Stapells et al., 1984). The method based on the ASSR amplitude, is called the F-ratio. In this test, the response power (amplitude²) of each modulation frequency is compared with a noise level estimate derived from a number of adjacent frequency bins around the considered modulation frequency, to determine if the response is statistically different from the background noise (Purcell et al., 2004). Another test to determine whether a recorded response is significantly different from the noise is the Hotelling's T^2 test. This test is based on the two-dimensional variance of the repeated measurements of the two-dimensional response (amplitude and phase) and is the multivariate counterpart of the t-test (Hotelling, 1931; Anderson, 1984). One can calculate the T^2 statistic using the following formula:

$$T^2 = N\,[\bar{x}, \bar{y}]'.S^{-1}\,[\bar{x}, \bar{y}] \qquad \text{(Equation 1)},$$

where N is the number of paired measurements x_i and y_i, $\bar{x}$ and $\bar{y}$ are the means of the paired measurements x_i and y_i and S is the covariance matrix of the means $\bar{x}$ and $\bar{y}$ of the paired measurements. Using T^2, one can determine whether a response mean is statistically different from zero (Picton et al., 2003).

3.4 Stimuli

3.4.1 Stimuli to evoke the ABR

ABRs belong to the subgroup of early latency responses and are onset potentials caused by the synchronous firing of nerve fibers. In order for the response to be measurable, two conditions must be met: a sufficient amount of fibers (condition one) need to fire synchronously (condition two). When a small number of fibers fire, the amplitude of the response will not be de-

tectable with surface electrodes. If a large population of fibers does fire, but the action potentials are smeared over time, the potentials will not be summed and again will not be detectable. This is called auditory neuropathy/dyssynchrony (Emara & Gabr, 2010; Picton, 2013).

The most optimal stimuli to meet these two conditions are broadband transient stimuli presented at low repetition rates (<20-30 Hz). Transient stimuli are characterized by an abrupt or rapid onset, theoretically containing all frequencies (Canale et al., 2006). A main disadvantage of ABR resulting from this stimulus characteristic is the lack of frequency specificity due to their broad excitation of the basilar membrane (BM). Stimuli with better frequency specificity are also in use to evoke ABRs, at the expense of their short duration that leads to smaller amplitudes of the response. Therefore, the elicited response of more narrowband stimuli is harder to detect (Stürzebecher et al., 2006). Because there is an important trade-off between stimulus duration and frequency specificity (Hall, 1992), one should always compromise between a stimulus that is well defined in time or in frequency, as both cannot be obtained simultaneously. Additionally, both input and output compensation (see Don et al., 1994) exist to obtain a more synchronous ABR. Input compensation is realized using rising frequency chirps that compensate for the traveling wave delay in the cochlea. These stimuli enable the inclusion of activity from lower cochlear frequency regions. All stimuli that are captured in this paragraph and thus are frequently used in ABR measurements will now be described in more detail.

3.4.1.1 The click

The click is a transient signal with a broad frequency range, which is produced by applying a single rectangular electrical pulse to the transducer (ISO 389-6, 2007). Figure 4 shows the amplitude-frequency spectrum of a 100 µs click. Because clicks excite a wide frequency range on the BM, this stimulus excites a substantial number of nerve fibers (Pinto & Matas, 2007). However, due to naturally occurring phase cancellations across the summed responses from AN fibers contributing to the AEPs (Don & Eggermont, 1978), it only gives information about the frequency range 2000-4000 Hz. The information on the auditory sensitivity across this audiometric range is very important, because it encloses the speech frequency region (Hall, 1992). The major disadvantage of the click is that the stimulus and the evoked response are not frequency specific.

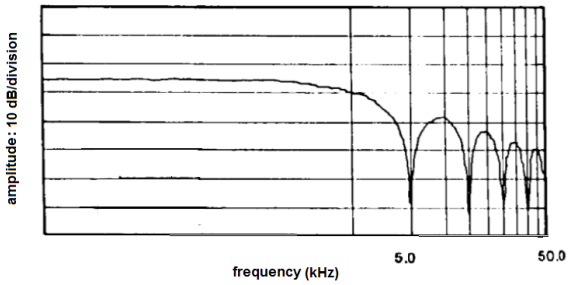

Figure 4. *Amplitude-frequency spectrum of a 100 µs electrical click.* Adopted from Gorga & Thornton (1988).

3.4.1.2 The rising frequency broadband chirp

The phase cancellations mentioned above, originate through a delayed traveling wave from the base of the cochlea to the apex. The neural elements along the basal part of the BM (high frequencies) are excited a few ms before the neural elements along the apical part (low frequencies) (e.g. von Bekesy, 1960). The amplitude of the AEP reduces because of this temporal smearing of the summed output from the AN. Additionally, as already mentioned, responses to broadband transient stimuli are mainly generated by high-frequent auditory channels alone (e.g. Don & Eggermont, 1978) because of lower traveling wave velocity in the apical region of the cochlea (Wegner & Dau, 2002). This reduced synchrony can partly be compensated for by a chirp in which the higher frequencies are delayed relative to the lower frequencies (Elberling et al., 2010) to produce simultaneous displacement maxima on the BM. In this way, contributing activity is extended to lower cochlear frequency regions (Wegner & Dau, 2002).

The internal spectral timing of the chirp must be estimated and designed by a temporal model of the cochlear-neural delay (Elberling et al., 2007). Different models, based on electrophysiological data, have been established and examined in literature to obtain the most efficient chirp (e.g. Dau et. al, 2000; Fobel & Dau, 2004; Elberling et al., 2007, Elberling & Don, 2008 and Elberling & Don, 2010). Based on these data, latency vs. frequency functions are constructed as a mathematical formulation of the model that can be described by the following general function (Anderson et al., 1971; Eggermont, 1979; Neely et al., 1988):

$$\tau = k.f^{-d}, \qquad \text{(Equation 2)},$$

where τ is the latency (in seconds), f the frequency (in Hz) and k and d are constants. Elberling et al. (2007) and Elberling & Don (2008) developed the level-independent Don-chirp (later referred to as the CE-chirp) based on click-evoked derived-band ABR wave-V latencies (Don et al., 1998; Don et al., 2005). In the latency-frequency function of this model, k and d have the

values 0.0920 and 0.4356 respectively. This model is shown in figure 5, together with other models of the cochlear-neural delay. From these latency-frequency functions, the corresponding frequency-dependent phase delay for the different chirps can be calculated. Chirps can then be constructed either in the time domain or in the frequency domain. The frequency domain method is described by Stürzebecher et al. (2006) and Elberling et al. (2007).

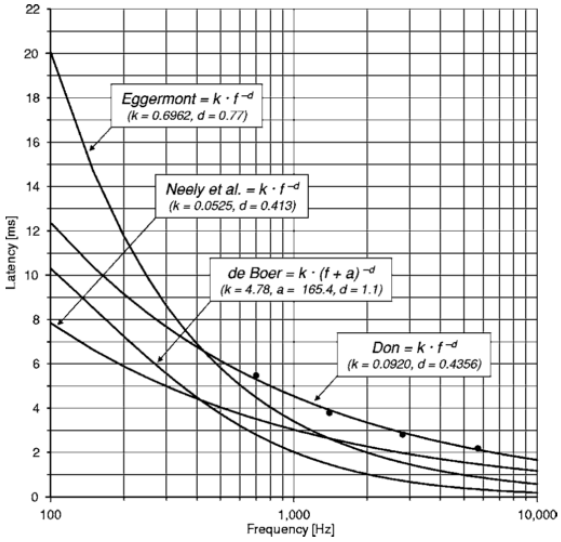

Figure 5. *Latency frequency functions and their parameters, from different electrophysiological studies to design chirp stimuli.* (1) narrowband CAP (Eggermont, 1979), (2) toneburst ABR (Neely et al., 1988), (3) narrowband ABR (Don et al., 2005) and (4) cochlear model (de Boer, 1980). Adopted from Elberling et al. (2007).

The chirp is shown to result in higher response amplitudes than the click in the auditory CAP, the ABR as well as the ASSR (Dau et al., 2000; Elberling et al., 2007). However, there is a disadvantage attached to chirp stimuli at high stimulation levels. Because the chirp excites a broader frequency area than the click, spread of excitation strikes earlier, resulting in decreased efficiency at higher stimulation levels (Elberling & Don, 2008). In the phenomenon of spread of excitation, the excitation on the BM broadens at high levels compared to a precise location of excitation at low levels. This results in desynchronisation of neural excitation and consequently lower response amplitudes (Elberling & Don, 2008; Elbering & Don, 2010; Fobel & Dau, 2004).

Additionally, several studies have compared the different chirps to determine which chirp is most efficient to obtain better AEPs. A level-dependent chirp, which is longer the lower the stimulus level and shorter the higher the intensity level, was demonstrated to be more efficient than a level-independent chirp, whose waveform is constant at different levels (Elberling et al., 2010; Fobel & Dau, 2004). The Don-chirp/CE-chirp, which is level-independent, was demonstrated to generate the largest ABR at 40 dB nHL, but not at 20 and 60 dB nHL. It was suggested that at higher levels upward spread of excitation and at lower levels an increased change of the cochlear-neural delay with frequency (which is not taken into account by the CE-

chirp) are the responsible mechanisms for this finding (Elberling et al., 2010). Also Elberling et al (2007) demonstrated that the Don-chirp/CE-chirp at 50 dB nHL was significantly more efficient in evoking ASSRs than other chirps. At higher or lower noise levels, the level-specific chirp would thus be most efficient because it does take into account the upward spread of excitation and changes in cochlear-neural delay with level (Elberling & Don, 2010).

3.4.1.3 The toneburst

The toneburst is a sinusoidal signal filtered by a time window with a duration of less than 200 ms (ISO 389-6, 2007). Figure 6 presents the time waveform and the amplitude-frequency spectrum of a 2 kHz toneburst gated with a 4 ms Blackman window. These stimuli only activate the neural units on the BM of which the characteristic frequency matches their nominal frequency (Hall, 1992). Because the toneburst represents a compromise between the desired frequency specificity and the required temporal brevity (Canale et al., 2012), this stimulus is most frequently used to generate a frequency-specific ABR (Hall, 1992). The reverse side of the medal, however, is that a short rise time causes spectral splatter: a spread of energy to frequencies adjacent to the nominal frequency (Hall, 1992). Furthermore, there is less synchrony in BM activation because the activated frequency regions are small (Canale et al., 2012), which in turn evokes response amplitudes that are typically only 70% of the click ABR amplitude, doubles the recording time to achieve the same SNR (Ferm et al., 2013) and complicates the identification of the different waves in the response (Rodrigues et al., 2013).

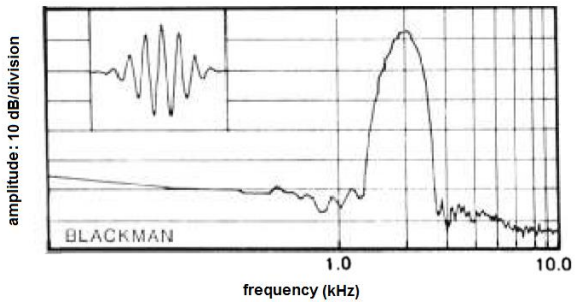

Figure 6. *The time waveform and the amplitude-frequency spectrum for a 2 kHz toneburst having 2 ms rise- and fall times and no plateau.* Adopted from Gorga & Thornton (1988).

The time window with which the sinusoidal signal is filtered has rise- and fall times of only a few cycles and a brief or no plateau. For example, the 2-1-2 toneburst is shaped with a linear function: there are two cycles in the rise- and fall times and one cycle in the plateau. This toneburst is seen as a compromise between a short onset and a long one to minimize the spectral splatter (Canale et al., 2012). The toneburst can also be shaped with a non-linear gat-

ing function, e.g. a Blackman window. Although the difference between the linear and the Blackman window was demonstrated to be not substantial, the latter window seems to be slightly better (Purdy & Abbas, 2002). Dagna et al. (2014) attribute the small superiority of the Blackman window over the linear window to its characteristics: 1 ms equal rise- and fall times and no plateau. In this way, it forms a good compromise between frequency specificity and temporal brevity and can thus be used to improve response synchrony while maintaining place specificity (Purdy & Abbas, 2002). Furthermore, this window has less sideband energy than equivalent-length Hamming and Hanning windows: the first side lobe contains energy at -58 dB relative to the energy in the main lobe (Rasetshwane et al., 2013).

3.4.1.4 Narrowband CE-chirps

Narrowband CE-chirps are octave-band limited CE-chirp stimuli centred around 0.5, 1, 2 or 4 kHz and battle toneburst stimuli in evoking frequency-specific ABRs. Narrowband CE-chirps are assumed to evoke larger frequency-specific responses due to the traveling wave delay compensation built into the octave band filter. Furthermore, this chirp has a wider bandwidth than the toneburst, which will increase the synchronization of the nerve fibers over a greater area of the BM. This should allow frequency-specific ABR tests to be acquired in a time closer to that of click ABR tests (Ferm et al., 2013). This advantage of the narrowband CE-chirp over the toneburst is more apparent at lower frequencies, because the longer stimulus rise time of the toneburst at low frequencies leads to a less well synchronized response (Ferm et al., 2013). Elberling & Don (2010) state that the narrowband CE-chirp centred around 4 kHz, like the broadband CE-chirp, produces the most optimal response at and around 45 dB nHL.

Several studies have indeed found that narrowband stimuli evoke larger ABR wave-V amplitudes than their tonebursts counterparts (e.g. Ferm et al., 2013). However, at high levels (80 dB nHL) the reverse was demonstrated in the study of Rodrigues et al. (2013). This decrease of chirp ABR amplitude at higher levels could be due to upward spread of excitation (see 3.4.1.2). Another disadvantage is that spectral splatter due to the broader activation on the BM could render the narrowband CE-chirp less frequency-specific compared to the toneburst (Elberling et al., 2007; Gøtsche-Rasmussen et al., 2012).

3.4.2 Stimuli to evoke the ASSR

ASSRs, in contrast, are electrophysiological responses evoked by periodic continuous stimuli modulated in amplitude and/or frequency according to a fixed (or sweeping, see 3.4.2.2) frequency or series of stimuli with sufficiently high repetition rates in order for the responses to

successive stimuli to overlap. The consequence is a periodic response consisting of discrete frequency components with stable amplitude and constant phase relative to the repeating stimulus (Stapells et al., 1984), for as long as the stimulus is turned on. In other words, the response is phase locked to the modulation frequency of the carrier or the repetition rate due to the synchronous discharge of the auditory neurons in the brainstem (Canale et al., 2006). Therefore, ASSR are also often referred to as envelope following responses. Two stimuli that are frequently used in ASSR measurements will be described in more detail below.

3.4.2.1 Fixed amplitude modulation

A pure tone, whose amplitude is modulated according to a fixed frequency, is called an amplitude modulated (AM) tone. This stimulus was first used by Campbell et al. (1977) to evoke ASSRs and can be generated by the following formula ($f_c \gg f_m$):

$$S = a[1 + m\sin(2\pi f_m t)]\ \sin(2\pi f_c t) \qquad \text{(Equation 3)},$$

where a is the amplitude of the stimulus, m is the modulation depth ($0 \leq m \leq 1$), t is the time (in seconds), fm is the modulation frequency and fc is the carrier frequency of a pure tone (Picton et al., 2003). Using trigonomic formulas, *S* can be rewritten as the sum of three components at f_c, $f_c + f_m$ and $f_c - f_m$ (Joris et al., 2004):

$$S = a\sin(2\pi f_c t) + \frac{a m}{2}[\sin(2\pi (f_c - f_m)t + \frac{\pi}{2}) + \sin(2\pi (f_c + f_m)t - \frac{\pi}{2})] \qquad \text{(Equation 4)}$$

The frequency spectrum of the AM tone contains of these three components: the carrier frequency and two sideband components which are separated from the carrier with the modulation frequency. The carrier frequency determines which part of the BM is stimulated and the modulation frequency or the rate is the frequency in the spectrum where the ASSR is detected (see 3.3.2). The stimulus thus only activates a very narrow area on the BM and therefore evokes highly frequency specific responses. Again, because of this, the response amplitude is low and the test time increases (Stürzebecher et al., 2006). Besides a pure tone, a noise stimulus can also be used as the carrier signal, whose amplitude is modulated by a periodic signal (e.g. Purcell et al., 2004). In this case, the reverse is true: because the noise spans a wide frequency range, a broad region on the BM is activated. Therefore, the compound response amplitude is high, which diminishes the test time. However, like in the click, phase cancellations caused by different BM characteristics reduce this advantage. Additionally, the response is not frequency specific.

3.4.2.2 Sweeping amplitude modulation

The term sweep (not to be confused with the 'sweep' that is a composition of several epochs) indicates that some aspect of the stimulus is continuously changed across a specific range (Purcell et al., 2004). This technique can be used to record the effect of a stimulus parameter on the ASSR, rather than making multiple separate recordings to different parameter settings (Regan, 1973, 1989). Thus, to assess the human brain's ability to respond to rapidly changing sounds, ASSRs can either be recorded to several stimuli whose amplitudes are modulated at different frequencies each time or either to a stimulus with a sweeping modulation frequency. In our study, the second possibility is applied, based on Purcell et al. (2004). In the latter study a 30.72 s long AM noise sweep of modulation frequencies from 20 to 600 Hz with a modulation depth of 25% was applied to measure the ASSR (for results, see 3.4.2.3). Because this stimulus changes over time, the amplitude and phase of the response is not constant and therefore 'ASSR' is not the correct designation. But, because the modulation frequencies used in the study were fast relative to the rate of change of the modulation frequencies, the responses are closer to ASSRs than to any other AEPs.

These AEPs cannot be adequately represented in the time domain and therefore need to be analysed in the frequency domain. The Fourier analyzer (see 3.3.2) can react quickly enough to follow this changing stimulus parameter of the signal and this renders the sweeping technique relatively easy to apply (Picton et al., 2003). Purcell et al. (2004) hypothesized that it should be possible to distinguish between brainstem and cortical problems by analysing the amplitude and latency in different frequencybands of the response. Another advantage is that one can repeat the sweep, calculate an average of the 'response to stimulus parameter' graphs, and smooth this averaged graph. When the shape of the graph is more important than the individual points, this technique is much more efficient than multiple individual measurements (Picton et al., 2003). One disadvantage is that the frequency resolution of the analysis depends on the applied low-pass filter to detect changes in response amplitude, and this might lead to increased noise in the recordings (Picton et al., 2003).

3.4.2.3 The effect of the stimulus modulation frequency on the ASSR amplitude

Stimuli to evoke the ASSRs are thus mostly modulated in amplitude (or frequency). The stimulus modulation frequency is one of the most important factors influencing the ASSR amplitude. Several studies have shown that ASSRs can be obtained for a wide range of modulation frequencies (30-190 Hz, Cohen et al., 1991; 20-600 Hz, Purcell et al., 2004; 2-400 Hz, Rees et al., 1986). The response amplitudes generally decrease with increasing stimulus rate, but near 40

Hz and between 80 and 120 Hz the response is enhanced. Therefore, the most extensively studied ASSR is evoked by stimuli with these modulation frequencies (e.g. Picton et al., 2003). Near 30 Hz and 70 Hz, a non-significant minimum in the response amplitude is obtained (Purcell et al., 2004). After 500 Hz, the responses of waking and sleeping subjects to 25% AM noise modulated at 20-600 Hz at 60 dB SPL in the study of Purcell et al. (2004) became insignificant. At higher modulation frequencies, responses keep decreasing and above 1500 Hz, practical no responses are measured anymore (Picton, 2013). The EEG noise also decreases with increasing rate or modulation frequency and therefore the SNR can actually increase (Picton et al., 2003).

Purcell et al. (2004) state that there are at least two subsystems to generate the ASSRs: the auditory brainstem and cortex, with cortical regions contributing more than brainstem generators at lower modulation frequencies or rates. Accordingly, Picton (2013) suggests that at high modulation frequencies, responses are more likely to originate from the cochlea than the brain. Thus, the responses originate from more central structures on the auditory pathway when using lower modulation frequencies (30-60 Hz, latency of about 30 msec (Cohen et al., 1991)) and from more peripheral structures when using higher modulation frequencies (90-95 Hz, latency of about ten msec (Cohen et al., 1991)). This happens because in the auditory stations on the pathway, sequential low-pass filtering occurs: the lower stations respond to a wide range of frequencies (e.g. 40 Hz and 80 Hz), while the higher stations respond to a decreasing range (e.g. only 40 Hz). The auditory cortex and brainstem have different response characteristics and latencies and the total net response determines the amplitude at a specific modulation frequency.

3.5 ABR vs. ASSR

To summarize, the main differences between the two objective methods that have been illustrated in the previous sections, are described in table 1.

Table 1. *Differences between the ABR and the ASSR.* AM = amplitude modulated, FM = frequency modulated, MM = mixed modulated (AM and FM) and f_m = modulation frequency.

		ABR	ASSR
Stimuli	General	Transient or at low repetition rates	Sustained/continuous and periodic or at high repetition rates
	Most common	• Click • Toneburst • Chirp	• AM stimuli • FM stimuli • MM stimuli
Response		Onset potential	Sustained, periodic and phase-locked to the f_m
Representation		Time domain	Frequency domain

Frequency specificity	Lower	Higher
Parameters	Amplitudes and latencies of wave-I to V	Amplitude and phase of the spectral component on f_m
Analysis	Visual interpretation of waveforms, subjective	Statistical test of the probability of a response, objective

Chapter 4: Research questions

4.1 Introduction

Many investigations clearly have demonstrated the mechanism of HHL and thus dismiss the general belief that TTS causes no permanent damage. Furthermore, possible consequences of frequent noise exposure have been shown to be tinnitus and hyperacusis. These three symptoms (TTS, tinnitus and hyperacusis) are frequently reported in studies concerning the effects of recreational noise exposure, which assess the self-reported hearing with HQs in adolescents and young adults. Some of these studies discuss the use of personal audio players, while others describe discotheque attendance. Both kinds of studies report substantial risks for HHL and the combination of both kinds of noise exposure may thus pose even a greater risk for the hearing system of young people. Additionally, as these people grow older, they may be potentially exposed to occupational noise and other noisy environments, which further increase the risk at HHL and HL itself.

Supra-threshold ABR measurements of the AN are demonstrated to be more sensitive to reveal HHL because HHL selectively damages AN fibers that respond to high-level sounds. In humans, it is not possible to conduct experiments in controlled environments, as is commonly done in animals, and therefore HQs must be used to assess the amount of noise exposure. All together, few studies have conducted objective measurements in people with possible HHL to diagnose this and therefore, we joined this small amount of studies. More specific, ASSR measurements were, until today, not yet obtained for this kind of experimental design, while the ASSR has been hypothesized to be a robust measurement of HHL in humans (Shaheen et al., 2012) and (high-frequency) ASSR could offer a more robust assessment of the AN, because wave-I of the ABR is rather hard to detect.

4.2 Hypotheses

The two main hypotheses of this study were the following:

1. Subjects who are more frequently exposed to recreational (and occupational) noise and not always involve themselves with protective behaviour have detectable differences in their suprathreshold short-latency ABRs and ASSRs, when compared with participants who are less often exposed to this kind of noise and/or do protect themselves against hearing damage.

2. Wave-I of the ABR (generated by the distal part of the AN) is correlated in some way with the ASSR at higher modulation frequencies (that elicit responses from more early stages in auditory processing, like the AN).

Chapter 5: Methods

5.1 Introduction

In this chapter the practical part of this study will be explained. Two testing phases, wherein the same subjects participated, are described. The first measurement phase, which served as a pilot test to determine the final parameters for the second testing phase, took place in springtime 2014 (not further described). The second phase took place in August, September and October 2014. First, the subjects will be presented to the reader, followed by a description of the threshold measurements, the HQ and the Digit Triplet Test (DTT). To detect potential HHL, the supra-threshold objective measurements ABR and ASSR were subsequently done to different stimuli and electrode configurations. The applied stimuli and their calibration, the recording and processing of the responses and the analyses of both objective methods will be described.

5.2 Subjects

Thirteen NH healthy young adults between the age of 20 and 28 ($\bar{X}$ = 22.150 years; σ = 2.001, range = 7.333 years) participated twice in this study (seven females and six males). Most of the subjects were students at a university or college, a few were working. For this study, people were supposed to be NH and therefore as young as possible, to avoid presbyacusis. Subjects were all volunteers, recruited by means of the social media. All tests were conducted in the department Experimental Oto-Rhino-Laryngology of the University of Leuven, Belgium. When test subjects arrived at the department, they were first verbally informed about the course of

the test and then read and signed an informed consent, approved by the Medical Ethical Commission. All measurements were done in the Industrial Acoustics Company GmbH (IAC) sound-insulated, electrically and magnetically shielded room. The total test time in the second measurement phase was around 108 minutes: six x six minutes for the short duration stimuli (see 5.6.1.1), 52 minutes for the sweep (see 5.6.1.2), and for some subjects two x ten minutes for the AM noise (see 5.6.1.2). The preparation and the threshold measurements (45 minutes) (see 5.3), the actual test time (108 minutes) and the time afterwards to take off the electrodes and clean the skin (ten minutes) taken together, the total time the subjects spent with us, was approximately two and a half hours. In appendix B an overview is given of the number of subjects in the different conditions described below.

5.3 Threshold measurements

In the first testing phase, subjects' hearing thresholds to pure tones were checked by means of pure tone audiometry of both ears to control their normal hearing. The PTA was completed with a portable audiometer (Madsen Elektronics, type Midimate 622) and a TDH-39 headphone. Thresholds were assessed by means of the shortened version of the ascending method (five up, ten down) described in ISO 8253-1 (2010). Their hearing thresholds were equal to or better than 20 dB HL for the range of frequencies 250-8000 Hz.

In the second testing phase, subjects' hearing thresholds for the short-duration stimuli (see 5.6.1.1) were checked in the test ear by means of APEX software (version three) (Francart et al., 2008). The stimuli were presented monaurally to the subjects by the ER-3A insert-phone. Thresholds were defined using the full version ascending method described in ISO 8253-1 (2010), with a step size of five dB. In this method, the first presentation should be at an intensity level clearly above the individual threshold (85 dB p-peSPL). When a response was obtained (a raise of the hand), the level was decreased by ten dB. When no response was obtained, the level was increased by five dB. The individual threshold was defined at the level where three responses are observed.

5.4 HQ

In addition to the testing in the sound insulated room (see 5.7.1), the participants afterwards completed a HQ at home to quantify their noise exposure background: the amount of noise-exposure they have been exposed to in their daily life for the past five years. The studies of Feder et al. (2013), Tung & Chao (2013) and Vogel et al. (2010) were used as an inspiration to

compose this HQ. It is elucidated in appendix C, which components from the studies are incorporated and for what reason. In summary, our HQ contains three main sections: the first gauges general health information about the history of ear problems, HL, tinnitus, tympanostomy tubes and hearing problems in the family. The second section is meant to find out the amount of noise subjects have been exposed to for the last five years. It asks for the frequency and the duration of visits, the intensity of the music, protective and risk behaviours and temporary symptoms that are associated with HHL in festivals, discotheques/parties and concerts. In addition, it questions portable audio player use (how many years, frequency, duration, intensity, locations) and it considers noisy hobbies and other activities in noisy environments. The last section contains self-evaluative questions considering complaints that indicate hearing difficulties and an estimation of the amount of noise in the subjects' daily lifes. The HQ is included in appendix D. The scoring of the HQ is indicated in yellow. Each possible answer was given a certain score, with answers indicating higher noise exposure connected to higher scores. This allowed us to divide the participants into two groups that were compared to each other with respect to the AEPs.

5.5 DTT

After the AEP measurements (see 5.7.1) the participants also underwent the Digit Triplet Test (DTT) at home to assess speech discrimination in noise. The DTT is a fast speech-in-noise self-test, which can be done over the internet through domestic audio equipment and is therefore highly advantageous for screening purposes. A high sensitivity and specificity to detect (supra-threshold) high-frequency HL, which is specifically present in HHL, was proven. 27 triplets of numbers were presented by means of an up–down adaptive procedure with steps of two dB. The speech-shaped noise level was fixed at 65 dB HL and the first triplet was presented at zero dB SNR. All three numbers were supposed to be identified correctly to alter the SNR. After the last response was obtained, the SNR of the (not-presented) 28^{th} triplet was determined. The speech reception threshold (SRT) was calculated by averaging the dB SNR values from presentations seven up to and including 28 (Jansen et al., 2013).

5.6 Stimuli

5.6.1 Characteristics

5.6.1.1 ABR stimuli

In the first testing phase, one AM tone at a low modulation frequency (30 Hz) to assess the ABR was presented to the subjects. Since the AM tone is a typical stimulus to evoke the ASSR and not the ABR, a sufficiently low rate was chosen to be able to represent responses clearly in the time domain. Because the responses were not clear, these results were not incorporated in our study. To obtain more clear responses in the second testing phase four different short-duration (transient or frequency-specific) stimuli that are more frequently used in ABR measurements were presented to the subjects. The response waveforms of the broadband stimuli served as a reference for the frequency-specific responses that are more difficult to interpret. The different properties of these stimuli are given in table 2.

Table 2. *Properties of the stimuli to evoke the ABR used in the second testing phase of our study.* Stim. = stimulus, f_c = carrier frequency, f_m = modulation frequency, I = intensity, MD = modulation depth, TB = toneburst, Pol. = Polarity, alt. = alternating.

			ABR			
Stim.	f_c	f_m (Hz)	I (dB nHL)	Duration	Presentation time	Pol.
Click[1]	Rectangular electrical pulse	40	50	100µs (rise and fall times less than 25µs)	6 min. (14400 presentations)	alt.
TB	Blackman window on a 4 kHz sinusoid	40	50	2ms	6 min. (14400 presentations)	alt.
CE-chirp	broadband	40	50		6 min. (14400 presentations)	alt.
4 kHz chirp	octaveband filtered CE-chirp around 4 kHz	40	50		6 min. (14400 presentations)	alt.

[1] (ISO 389-6, 2007)

The CE-chirp was chosen because the studies of Elberling et al. (2007), Elberling et al. (2010) and Elberling & Don (2010) all demonstrated that the delay model whereupon the Don-chirp/CE-chirp is based (see 3.4.1.2), is the most efficient model at moderate intensities around 50 dB nHL. The original broadband CE-chirp was designed as described by Elberling et al. (2007). This stimulus has a flat electrical amplitude spectrum within five octave-bands and ranges from 350 to 11300 Hz (minus three dB points). The lower amplitude-frequency roll-off corresponds to the lower part of a 500 Hz octave-band filter. The higher amplitude frequency roll-off corresponds to the higher part of an 8000 Hz octave-band filter. The amplitude spectrum of the 4 kHz octave-band filtered CE-chirp corresponds to the standardized octave-band filter (IEC 61260, 1995; Elberling & Don, 2010). In figure 7(a), the electrical waveforms of the

CE-chirp and the octave-band CE chirps are shown and in figure 7(b), the corresponding amplitude spectra can be seen.

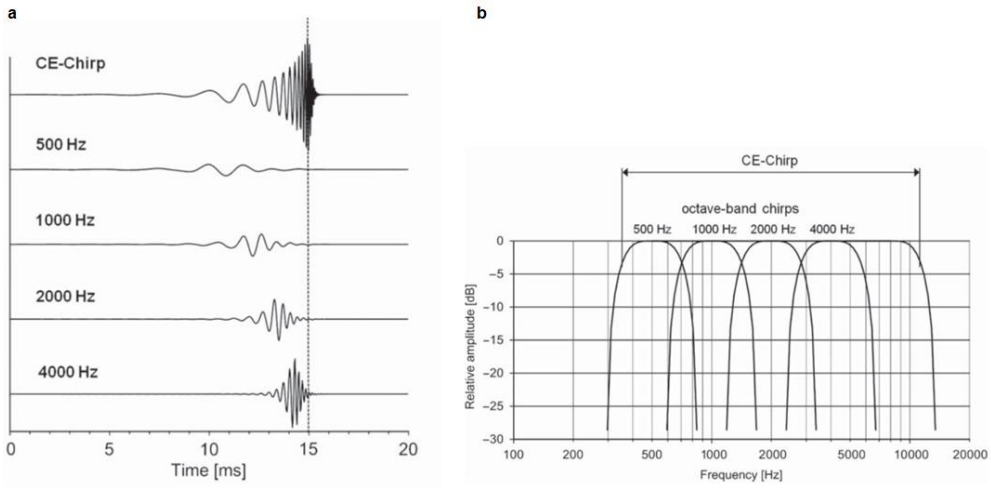

Figure 7. *The electrical waveforms and amplitude spectra of the chirp stimuli.* Left (a): the electrical waveforms of (from top to bottom) the broadband CE-chirp and the narrowband octave-band filtered chirps with a centre frequency of 0.5, 1, 2 and 4 kHz. The first and the last stimulus are used in our study. The amplitude scale is the same for all stimuli. Right (b): the amplitude spectrum of the electrical narrowband chirps relative to the CE-chirp. See text for further details (adopted from Gøtsche-Rasmussen et al., 2012).

The chirp stimuli were designed using the frequency-domain method (Elberling et al., 2007). This method is used when the spectral characteristics of stimuli are most important, because it allows the amplitude and phase of each harmonic in the spectrum of the chirp to be adjusted. By adjusting the phase, the final stimuli were designed to compensate for the cochlea traveling delay. By adjusting the amplitude, the frequency-specific octave-band chirp was designed and the amplitude spectrum of the CE-chirp was adjusted to compensate for the amplitude-frequency response of the ER-3A insert-phone (Elberling et al., 2012).

All short duration stimuli were assessed at a rate of 40 Hz. This rate was chosen because of the greater amplitude of AEPs at 40 Hz due to the superimposition of the successive peaks of the middle latency response (Stapells et al., 1984). All stimuli were presented with an alternating polarity to rule out transducer-dependent artefacts and to compare with existing literature. The click, toneburst, CE-chirp and 4 kHz chirp were all presented at 50 dB nHL to obtain responses from the high-SR as well as the low-SR population of fibers. The carrier frequency of the frequency specific stimuli was always set at 4 kHz, because this study assesses the AEP response characteristics of NH subjects with potentially HHL, which is the precursor of NIHL. NIHL is manifest in the audiogram as a dip at frequencies at and around 4000 Hz, is selective for the high frequencies, typically bilateral and symmetrical (Attias et al., 2014).

5.6.1.2 ASSR stimuli

In the first testing phase, the responses to two different sweeps (a 4 kHz octave band noise sweep and a 4 kHz pure tone sweep) at relatively high modulation frequencies (70-600 Hz) to evoke the ASSR were assessed. The ASSR measurements of the first testing phase are not further described, because they only served as a pilot study for the second measurement phase. In the latter phase, the responses to one or three stimuli were assessed to evoke the ASSR. First, a sweep was again presented to the subject. Only the noise band carrier was tested again because the responses were greatest with this carrier and the high modulation rates (>300 Hz) were omitted because of very low response amplitudes. This noise band sweep was based on the study of Purcell et al. (2004). Besides, two amplitude modulated 4 kHz noise bands were presented to the subjects when permitted by time. This was done to obtain more clear ASSRs due to a longer recording time per modulation frequency. One AM noise was presented at 40 Hz, as this is a common tested modulation frequency in ASSR literature. The other AM noise was presented at 275 Hz to measure the AN. The different properties of these stimuli are given in table 3.

Table 3. *Properties of the stimuli to evoke the ASSR used in the second testing phase of our study.* Stim. = stimulus, f_c = carrier frequency, f_m = modulation frequency, I = intensity, MD = modulation depth, NB = noise band.

	ASSR					
Stim.	f_c	f_m (Hz)	I (dB A)	Duration	Presentation time	MD (%)
Sweep	NB 1 octave around 4 kHz	35-300	50	30x1.024s =30.72s	52 min (100 presentations)	100
AM	NB 1 octave around 4 kHz	40	50	10 min	10 min	100
AM	NB 1 octave around 4 kHz	275	50	10 min	10 min	100

For the sweep, 4 kHz was again chosen as frequency around which the octave band noise is centered. This choice was made because of the specific research design. The moderate intensity of 50 dB A again enables the contribution of the high-SR fibers, as well as the low-SR fibers, to the response.

5.6.2 Calibration

5.6.2.1 ABR stimuli

The short duration stimuli were calibrated in dB peak-to-peak equivalent sound pressure level (dB p-peSPL) by means of a 2250 Bruël & Kjær sound level meter and pre-amplifier and an artificial ear type 4152 with the Bruël & Kjær 1” pressure-field microphone type 4144. The remaining volume in the ear canal after applying the ER-3A insert-phone was simulated by a

2cc coupler. The equipment itself was calibrated by means of the sound level calibrator (Bruël & Kjær type 4230), which broadcasts a frequency of 1000 Hz at 94 dB SPL. The calibration was performed with RBA software. The artificial ear was connected to the sound level meter and an oscilloscope (LeCroy, W waveRunner HRO64Zi 400MHz 12-bit 2GS/s oscilloscope). Stimuli were presented using the RBA software to the ER-3A insert-phone that was connected to the 2cc-coupler in the artificial ear. A single stimulus was sent to the sound level meter and the output of this device was then displayed on the oscilloscope. In this way, the linear peak-to-peak value (In Volts) of the different stimuli could be read from the screen of the oscilloscope and the peak equivalent SPL value (in dB) of the different stimuli could be read from the screen of the sound level meter. By means of the sound level calibrator (1000 Hz, 114 dB SPL, Bruël & Kjær type 4230) correction factors could be calculated to obtain the dB p-peSPL values, since the actual intensity in dB SPL of this reference tone is known. To enable the possibility to calibrate these stimuli by means of the sound level meter (without the oscilloscope) in the future, correction factors between the measurements on the oscilloscope and the sound level meter per stimulus were also calculated. All calculations are included in table 4.

Table 4. *Calculations to determine the correction factors to obtain the dB p-peSPL values for calibration of the short-duration signals and correction factors between the oscilloscope and the sound level meter to perform calibration with the latter device.* Stim. = stimulus, Cal. = calibrator, TB = toneburst, SLM = sound level meter.

Stim.	dB SPL[1]	dB peSPL[1]	Mean p-p (V)[2]	Mean p-p (dB)[2]	dB p-pe SPL[3]	Correction factor (dB)[4]	SLM-scope[5]
Cal. 114 dB	114.1	117.2	1.212	1.67	114.10	112.43	-3.10
+ click (inverted)	76.3	100.6	1.279	-17.86	94.57		-6.03
4 kHz chirp	75	96.1	0.959	-20.36	92.07		-4.03
CE chirp	63	76.3	0.731	-42.72	69.71		-6.59
TB	83	101.4	1.97	-14.11	98.32		-3.08

[1] These are the values that could be read from the screen of the sound level meter. The dB SPL values were obtained with the LZF setting.

[2] These are the peak-to-peak values that could be read from the oscilloscope, linear and in dB. The values in dB are corrected for the sound level meter gain.

[3] The dB p-peSPL values were calculated by first adding the correction factor and the mean peak-to-peak value (in dB) of the stimulus and then subtracting the amplifier gain.

[4] The correction factor was calculated by subtracting the mean peak-to-peak value (in dB) from the dB SPL value.

[5] By subtracting the dB peSPL value from the dBp-peSPL value, future calibration could be performed with the sound level meter alone.

Second, the short duration stimuli were transformed to dB nHL by means of existing peRETSPL (peak-to-peak equivalent reference equivalent threshold sound pressure level) values. These values are obtained in literature by stimulating a transducer with a sound level that corre-

sponds to the hearing threshold of NH subjects. In this study, measurements were realized at 50 dB nHL, thus, if we consider these reference values to equal zero dB nHL, stimuli were presented 50 dB above these levels. In about half of subjects, a reference value that was not completely correct has been used. For the other half, corrections have been made. The first reference value together with the characteristic of the stimulus it applies to and the adjusted reference value together with the reason for adjustment are given in table 5.

Table 5. *0 dB nHL calibration values for the different stimuli used in our study.* Because the right values were not used from the beginning, a difference between the first (inadequate) values and the stimulus characteristic it applies to and the second (adequate) values together with the reason for adjustment is made. TB = toneburst.

Stim.	peRETSPL (in dB p-peSPL)	Characteristics of stimulus	Adjustment (in dB p-peSPL)	Reason
Click	35.5 (6 subjects)	rate 20 Hz	33.6 (7 subjects)[1]	rate 40 Hz
TB	31.7 (6 subjects)	2-1-2 4 kHz TB, rate 40Hz	26 (7 subjects)[2]	Blackman window
CE-chirp	32 (all subjects)[3]	/	/	/
4kHz chirp	32 (6 subjects)	CE-chirp	35 (7 subjects)[4]	4 kHz chirp

[1] The reference click specified in ISO 389-6 has a rate of 20 Hz, whereas the click we used had a rate of 40 Hz. Therefore, a correction was applied to the peRETSPL value, but only in seven of the subjects because this was only noticed later on. As the threshold tends to decrease with increasing repetition rate, the corrected reference value we used for the click was 33.6 dB p-peSPL. Thus, a correction factor of 1.9 dB was applied (mean of -1.7 for the TDH-39 and -2.1 dB for the HDA-800 specified in ISO 389-6) (Richter & Fedtke, 2005).

[2] In our study the toneburst was gated with a Blackman window, whereas the calibration value we first used was based on the reference toneburst at a rate of 40 Hz gated with a linear window (Fedtke & Richter, 2007). Therefore, the calibration value for 0 dB nHL was changed to 26 dB p-peSPL for the last seven subjects because this was only noticed later on. This value is the calibration value for a Blackman windowed toneburst, presented at 39.1 Hz and thus closer to our stimulus (BCEHP, 2008).

[3] Provided by PTB (Physikalisch-Technische Bundesanstalt, Braunschweig, Germany).

[4] It was not completely right to use the same calibration value for the 4 kHz chirp (narrowband CE-chirp) as for the CE-chirp. Therefore, the reference value (also provided by PTB) was adjusted for the remaining seven subjects to 35 dB p-peSPL for the 4 kHz chirp. These values were obtained in 25 NH subjects in accordance with the recommendations specified in ISO 389-9 (2009).

5.6.2.2 ASSR stimuli

The sweep was calibrated in dB A by means of the same equipment listed in 5.6.2.1. The stimulus was presented to the artificial ear and the sound level was measured with the sound level meter. Since the sweep is not stationary, the sound level was measured on the 95th percentile. A target value was defined in the RBA program and after the measured sound level was entered, the program calculated and applied a correction factor. This procedure was repeated until the chosen target and the measured sound level did not differ more than a half dB.

5.6.3 Generation and presentation

In figure 8, the measurement set-up to perform the stimulus presentation (and response recording) is presented. Stimuli were either generated on the laptop with RBA software, or programmed using MATLAB (R2012a) using custom scripts. Digital-to-analog conversion was per-

formed using the sound card RME Hammerfall DSP Multiface II with a sample rate of 32 kHz and 24-bit precision. The stimuli were presented to the individual by the ER-3A insert-phone and the TIPtrode which is used for stimulus presentation and response recording. The TIPtrode is demonstrated to enhance wave-I amplitude (see 3.3.1.2) (Bauch & Olsen, 1990).

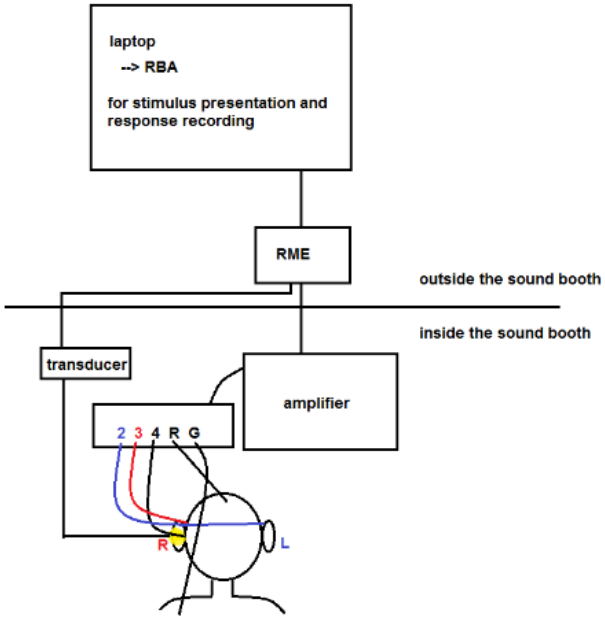

Figure 8. *A summary of stimulus presentation and response recording steps in the AEP measurements, shown separately for inside and outside the sound booth.*

5.7 Responses

5.7.1 Recording

The electrophysiological signal was picked up by four far field silver cup chloride electrodes with a diameter of ten mm and the TIPtrode. The EEG was recorded from the high-midline forehead (non-inverting electrode), the left and right mastoids, the right ear canal (inverting electrodes) and the clavicle (common/ground electrode) using three channels: ipsilateral (IL), contralateral (CL) and in-ear (IE). The participants were asked in advance to clean their right ear and to wash their hair. For electrode placement, the skin was scrubbed with an abrasive gel (Nuprep) and cleaned with alcohol gel. Scalp electrodes were applied to the skin with electrolytic paste (Ten 20) and tape. Inter-electrode impedances of the cup electrodes were measured with the Prep-Check PLUS device from General devices and were below five kOhm. The TIPtrode was placed in the right ear canal (except for one subject due to an injury in the ear canal), after the participant scrubbed his ear with the abravise gel on a cotton swab. The impedance of the TIPtrode was kept as low as possible, however, it was difficult to keep it below

five kOhm. The subjects were instructed to lie down in the electrically and magnetically shielded sound booth and to move minimally. They were subsequently asked to remove all electronic devices from their bodies, to not interfere with the test. For the AEP measurements, it was not allowed to sleep because stimuli were presented starting from rates of 40 Hz and sleep diminishes the amplitudes of the AEP at slow rates (Picton et al., 2003). The participants were allowed to watch a movie without sound. After the testing was done, the electrodes were removed and the residual electrolyte paste on the skin was cleaned with alcohol gel.

5.7.2 Processing

5.7.2.1 Processing of the ABRs

The electrodes were plugged into an electrode box, which was connected to the amplifier (Jaeger DC-Verstärker, Viasys Healthcare GMBH, SN 580045). This device gained the responses by a factor of 50000 (20 µV/V), which corresponds to an amplification of 94 dB. The device also applied common mode rejection based on the ground electrode and bandpass filtering between two and 20000 Hz. After that, analog-to-digital conversion was performed and the signals were transmitted back to RBA. During the recording, the signal was continuously stored on a hard disc. Furthermore, filtering with a fourth order butterworth filter between 45-2500 Hz, artifact rejection of epochs with the five percent greatest peak-to-peak amplitudes and averaging of periods (25 ms) over approximately 14 400 presentations were performed in Matlab (R2012a). Data collection was delayed by one ms to compensate for the acoustic delay by the long earphone tubing (ER-3A: 256 mm) (Elberling et al., 2012). ABRs to the chirps, clicks and toneburst were analysed in the time domain. The responses to the short duration stimuli were also analysed in the frequency domain by means of the FFT and the Hotelling's T^2-test (see 3.3.2).

5.7.2.2 Processing of the ASSR

The processing of the ASSRs occurred in the same way as the processing of the ABRs, except for a few elements. The applied filter in Matlab (R2012a) was a highpass filter with a two Hz cutoff frequency and the averaging occurred over epochs of 1.024 s (and not periods) over approximately 100 stimulus presentations. The responses to the sweep were analysed in the frequency domain. The FFT or the Fourier analyzer (with an integration window of one second) (see 3.3.2) was employed to extract the ASSRs from the average EEG 'sweep' fed to the system. The Hotelling's T^2-test was subsequently used to detect significant ASSRs (see 3.3.2).

5.7.3 Analysis

5.7.3.1 Parameters derived from the auditory brainstem response

For the ABRs, the following parameters were derived from the measurements. From the waveform obtained by averaging several responses in the time domain, the peak-to-peak amplitude of wave-I, wave-V, wave-V-I and wave-V/I were visually derived. For the CL electrode configuration, wave-I was not derived because auditory processing in the ANs does not occur bilateral and stimuli were presented to the right ear.

Hall (1992) presented two methods for the art of 'peak picking': selecting the peak as the point on the wave component with the largest amplitude (peak) or selecting the final data point on the wave preceding the slope of the following trough (shoulder). We applied the first method. Peak-to-peak amplitudes of wave-I were digitally calculated using Matlab between the peak and the following trough, after visually determining the ranges of these peaks and troughs. Matlab calculated the amplitude between the greatest value in the first range (peak) and the smallest value in the second range (trough). As the trough following wave-I was not always clearly present because wave-II was sometimes absent, it was not always possible to digitally determine the amplitude between the peak of wave-I and the through preceding wave-II. Therefore, Matlab took the following clear trough to calculate the amplitude. To determine wave-I amplitude consequently over subjects, we corrected these values visually by multiplication and division (see appendix G(b)). This problem of missing peaks is quoted in literature, but no practical solution is given (Hall, 1992). Wave-V was digitally calculated by Matlab from peak to the following *deepest* trough, also based on the ranges that were visually determined. As wave-V was always clearly visible, no problems were encountered.

To clarify all this, the amplitudes of wave-I and wave-V of two subjects are determined in figures 9 and 10 as an example. In the first subject (figure 9), all waves are clearly present and therefore wave-I amplitude can be calculated between the peak of wave-I and the trough preceding wave-II. However, in the second subject (figure 10), only three waves are visible and therefore the amplitude of wave-I is calculated between the peak of wave-I and the trough preceding wave-III. In this example, the calculated wave-I amplitude was therefore divided by two. The peak-to-peak amplitude of wave-V is in both examples determined between the peak of wave-V and the following deepest trough.

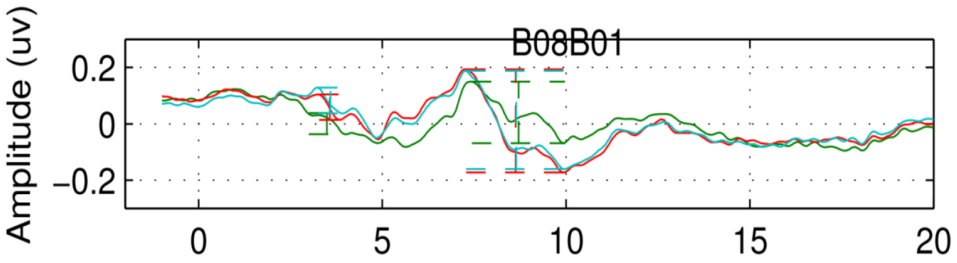

Figure 9. *Demonstration of how peak-to-trough amplitudes of wave-I and wave-V were determined when all waves were clearly present.* The red line represents the ipsilateral response, the green line represents the contralateral response and the blue line represents the in-ear response.

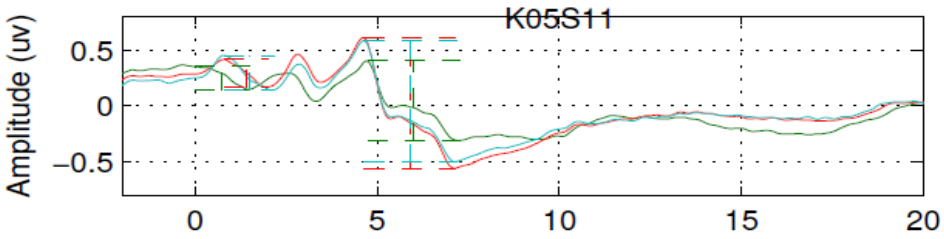

Figure 10. *Demonstration of how peak-to-trough amplitudes of wave-I and wave-V were determined when all waves were not clearly present.* The red line represents the ipsilateral response, the green line represents the contralateral response and the blue line represents the in-ear response.

In literature, the wave-V/I ratio is frequently incorporated and is demonstrated to be an important parameter to detect HHL in humans (Schaette & McAlpine, 2011). Additionally, this quotient reduces the variability in the responses and thus could be a more robust parameter than wave-V or wave-I alone. Therefore, this parameter was included in the statistical analysis. Furthermore, the wave-V-I peak-to-peak difference was calculated and also included in the statistical analyses. Finally, the (biased and unbiased) response amplitudes to the short duration stimuli were also calculated in the frequency domain to become new dependent variables to use for further analysis. In the unbiased response amplitude a noise estimate is substracted from the signal. When the responses to the short duration stimuli are analysed in the frequency domain, it is not possible to distinguish between the different waves. All amplitude measurements contain signal as well as noise.

5.7.3.2 Parameters derived from the auditory steady state response

For the swept ASSR, parameters were derived by calculating the mean response amplitude of the significant data points in different frequency ranges (from f_1 to f_2), using Matlab and the following equation:

$$Mean(\mu V) = \frac{\sum_{i=f1}^{f2} Ai}{N} \qquad \text{(Equation 5)},$$

where ΣA_i is the sum of the amplitudes per frequency bin in the desired frequency range (from f_1 to f_2) and N is the number of frequency bins in the frequency range that is taken into ac-

count. Seven different frequency ranges were assessed: 35-55 Hz, 40-40 Hz, 80-80 Hz, 75-90 Hz, 150-250 Hz, 150-300 Hz and 275-275 Hz. These ranges were chosen to evaluate different stations on the auditory pathway. The high frequency ranges were chosen because of the possible relationship with ABR wave-I, because higher modulation frequencies elicit responses with shorter latencies and thus from more peripheral auditory structures. The responses to modulation frequencies between 35-55 Hz and 40-40 Hz are thought to be generated by sources along the Heschl's gyrus (the auditory cortex) (Ross et al., 2003), while responses to rates between 75-90 Hz and 80-80 Hz are presumably generated by the brainstem (Purcell et al., 2004). A few times in the analysis, the parameter mean SNR is also applied. This parameter is calculated as in equation 5, but the amplitudes are replaced by the SNRs. All parameters contain signal as well as noise, as in the ABR parameters. The measurements were not converted to dB to enable an adequate comparison with the ABR parameters (also in μV). Additionally, in comparison with the ABR wave-V/I parameter, a ratio parameter for the ASSRs was calculated for the ranges 150-250 Hz on 35-55 Hz. For the responses to the additional AM noise stimuli modulated at 40 Hz and 275 Hz, the response amplitudes were derived from the frequency component on the modulation frequency in the spectrum.

5.8 Statistical analysis

In this study, besides the two main hypotheses, first two factors were assessed: electrode configuration (IL, CL, IE) and stimulus (ABR: CE-chirp, click, toneburst or 4 kHz chirp, ASSR: no comparisons could be made because of different units between the stimuli). These factors were analysed separately for significant effects on most dependent variables of the AEP. Because assumptions for parametric tests were not met (normality and homoscedasticity) for all variables due to the small test-group, non-parametric versions of these statistical tests were applied. All predictor variables were categorical and the outcome variable was always continuous. The factors stimulus and electrode configuration were analysed using the Friedman's ANOVA. This test is used when the different categories of the factor contain the same subjects (within-subject experimental design). If significance for an overall effect was met for a certain factor, it was assessed which category of the factor (e.g. which stimulus) caused this, because based on only the results of the Friedman's ANOVA, it was not clear where the difference was situated. These paired comparisons were assessed by means of the Wilcoxon signed-ranks test, which compares scores between two conditions consisting of the same participants (Field, 2009).

Second, the scores on the HQ have been visualised and based on the distribution two groups were made. In the low noise exposure group subject's scores were lower than the scores in the high noise exposure group. Higher scores mean a greater history of noise exposure and thus the high noise exposure group is the group that has had a higher risk at HHL for the past five years. The parameters of the ABR and ASSR were first (separately) assessed to have a relationship with the noise exposure scores theirselves, by means of bivariate correlation analysis. Again, because assumptions are hard to meet when using a small sample size, the Mann-Whitney U test was also applied to test for differences in AEP amplitudes between the two groups. Third, all ASSR and ABR parameters were compared by means of bivariate correlation analysis to find all possible r-values.

In addition to these ABR and ASSR analyses, possible confounding factors were assessed. Therefore, multiple regression analyses were carried out on the ABR amplitudes of wave-I with the thresholds for the short duration and the HQ scores as independent variables. This was done to check whether the amplitude of wave-I was not influenced by the individual threshold. To check whether the pure tone thresholds were not already affected by noise overexposure, the difference in these thresholds between groups was assessed with a Mann-Whitney U test.

All analyses were carried out using SPSS software (SPSS 17.0, Inc., Chicago, IL, USA). Multiple significance tests were conducted and therefore, the level of significance was adjusted to 0.01 instead of 0.05 to control the overall type-I error (rejecting the null-hypothesis when it is not false). Because the simple Bonferroni correction (α/number of tests performed) tends to be too strict when many test are conducted, the α-level in our study would reach a value very close to zero. This would prevent us to present a correct image of our results by lowering the power of the test and thus increasing the probability of the type-II error (accepting the null-hypothesis when it is false and thus rejecting significant differences). Therefore, we decided to lower the α-level to 0.01 as an interim solution, because other post-hoc corrections (like the Games Howell correction) are restricted to parametric versions of ANOVA (which we do not apply) (Field, 2009). To assess the importance of the potential significance, a measure of effect size was incorporated. The effect size (*r*) was calculated by dividing the z-value of the non-parametric test by the square root of N (number of total observations). An *r*-value of 0.3 is the criterion for a medium effect size and 0.5 is the criterion for a large effect size (Field, 2009). As our study contains many dependent variables, not all results of statistical analysis on these variables are shown if not contributing to the results that already have been reported. The independent variables whose results are always demonstrated are the mean amplitudes in different frequency ranges of the ASSR to the noise sweep and the peak-to-peak amplitudes

for the different waves of the ABR (as analysed in the time domain), because these variables contain most information.

Chapter 6: Results

6.1 Introduction

The results of the analysis (as explained in 5.8) are presented in this chapter. Because the AEP measurements in the first testing phase served as a pilot test to decide which parameters were adequate to evoke AEPs concerning our research questions, only the AEP results of the second testing phase are shown. As described in the previous chapter, the ABR data were analysed in the time domain as well as in the frequency domain. However, only the results of the most frequently used analysis method (in the time domain) are presented, because the results of the analyses in both domains followed similar trends.

6.2 Threshold measurements

The individual results of the PTA and APEX threshold measurements are listed in appendix E. The APEX threshold measurements are described by their ranges, minima, maxima, means and standard deviations in table 6, while a mean pure tone audiogram of the tested ear is shown in figure 11. All subjects had thresholds equal to or better than 20 dB HL on the pure tone audiogram. Finally, there was no significant correlation between the 4 kHz pure tone threshold and the HQ scores (r=0.284, p=0.347).

Table 6. *Number of right ears, ranges, minima, maxima, means and standard deviations of the threshold measurements in testing phase 2.* The threshold measurements with the short duration signals are presented in dB p-peSPL.

Measurement	Stimulus	N	Range	Minimum	Maximum	Mean	SD
APEX	CE chirp	13	10,000	30,000	40,000	34,615	4,312
	Click	13	10,000	30,000	40,000	35,769	3,444
	NB chirp	13	15,000	20,000	35,000	26,923	4,349
	TB	13	15,000	20,000	35,000	25,769	4,494

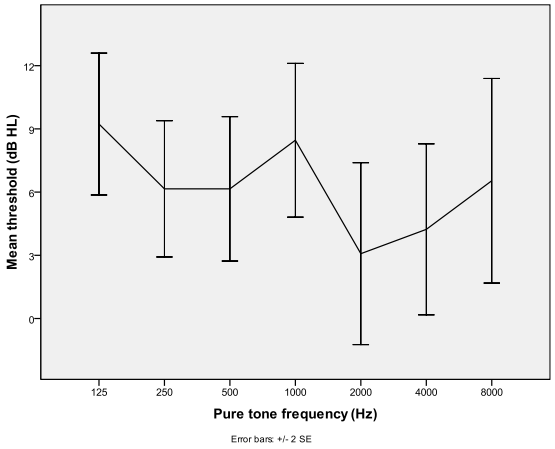

Figure 11. *Mean pure tone audiogram of the right ear of subjects in dB HL, with error bars (2 standard errors).*

6.3 Hearing questionnaire

As described before, a HQ concerning noise exposure was filled in by all subjects and two groups were made: one with relatively low noise exposure and one with relatively high noise exposure during the past five years. In figure 12, it can be seen that the scores follow a bimodal distribution. A score of 20 was regarded as the limit between groups. The low noise exposure group contains subjects with scores <20 and the high noise exposure group contains subjects with scores >20 (higher scores indicate a higher noise exposure). A Mann-Whitney U test confirmed scores were significantly different between groups (N=13, U=0, p=0.001, *r*= -0.834).

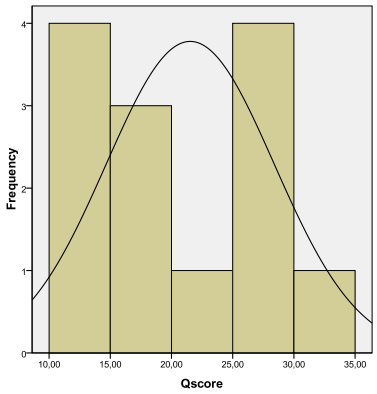

Figure 12. *Histogram of questionnaire scores (Qscore).* The thin line displays a normal curve.

6.4 Digit Triplet Test

After the AEP measurements, the DTT was conducted. The SRT for the test ear of subjects is given in appendix F(a). The scores range from -10.091 to -13 dB SNR, having in mind the precision of the test is around one dB (0.8 dB, Jansen et al., 2013). The correlation between the SRTs and the HQ scores was found to be 0.007 using linear regression analysis (F(1, 11)=0.001, p=0.981). In appendix F(b), a scatterplot of the relation between the SRT and the HQ score is

also shown. In addition, the Mann-Whitney U test demonstrated no significance difference in SRTs between the two groups (N=13, U=20.000, p=0.921).

6.5 Detecting confounding variables

First, multiple regression analysis was carried out on the amplitudes of wave-I (IL) with the thresholds for the short duration signals (toneburst, narrowband CE-chirp, CE-chirp and click) as measured by APEX and the scores of subjects on the questionnaire as independent variables. This was done to check whether the amplitude of wave-I was not influenced by the individual threshold and thus to exclude this factor as a confounding variable. In table 7, the results of this analysis are listed. It can be seen that the specific stimulus threshold never has a significant contribution to the multiple regression of wave-I amplitude and that correlations between these two variables are never significant. Therefore, stimulus threshold is probably not a confounding variable.

Table 7. *The results of the multiple regression analysis on the amplitudes of wave-I, with the threshold for the short-duration signals and the HQ scores as predictors.* Column 2 and 3: correlations between wave-I amplitudes and hearing thresholds and significance levels (1-tailed) per stimulus, column 4, 5 and 6: the degrees of freedom of the F-model, the value of R^2 of the model and its significance, column 7 and 8: the value of the predictor coefficient of the threshold parameter per stimulus together with its significance.

Stimulus	rThreshold-wave-I	p(r)	df	R^2 model	$p(R^2)$	$\beta_{threshold}$	$p(\beta_t)$
Click	0.237	0.255	(2,7)	0.072	0.770	0,004	0,527
Toneburst	-0.407	0.094	(2,9)	0.178	0.415	-0.027	0.197
CE-chirp	0.291	0.168	(2,10)	0.174	0.385	0,003	0,327
4 kHz chirp	-0.390	0.094	(2,10)	0.165	0.405	-0,004	0,190

In addition, it was assessed whether the pure tone audiometric thresholds were significantly higher for the group with a relatively high noise exposure then for the group with a relatively low noise exposure. If this is the case, the noise exposure would be assumed to have already slightly affected the thresholds of hearing, which also would influence the suprathreshold AEP measurements. The mean pure tone thresholds per frequency of both groups are shown in figure 13 and the results of the Mann-Whitney U test are shown in table 8.

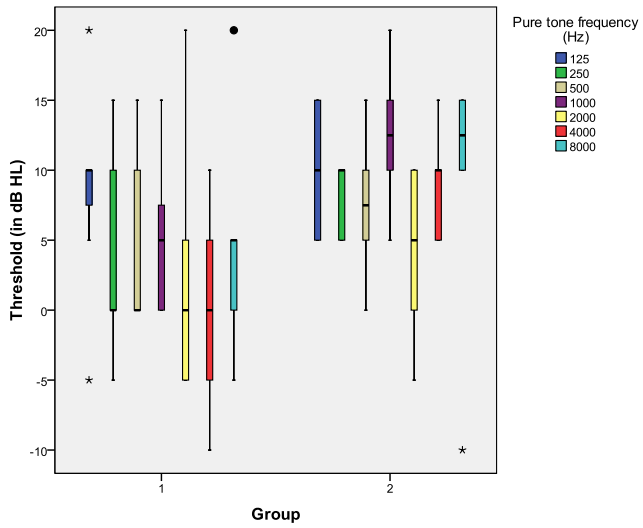

Figure 13. *Pure tone thresholds per frequency for subjects in the low noise exposure group (group 1) and subjects in the high noise exposure group (group 2).*

Table 8. *The results of the Mann-Whitney U test of the pure tone thresholds between groups.*

Group 2 > group 1	Pure tone frequency (Hz)						
Mann-Whitney U	125	250	500	1000	2000	4000	8000
N	13	13	13	13	13	13	13
U	19.000	14.000	15.000	7.000	15.500	5.500	12.000
p	0.850	0.319	0.403	0.054	0.469	0.024	0.200
r	-0.084	-0.294	-0.248	-0.567	-0.224	-0.633	-0.362

Because at 4 kHz a significant result was become at an α-level of 0.05, but not at an α-level of 0.01, the thresholds to the short duration signals were also assessed to be different between groups, because the toneburst and narrowband chirp are also presented at 4 kHz. However, there were found no significant differences between groups (results not shown). In the discussion, the meaning of these results for the interpretation of other effects is described.

6.6 ABR

6.6.1 General results

The descriptive statistics (ranges, minima, maxima, means and SDs) of the general ABR amplitudes are shown separately for wave-I, wave-V and wave-V-I per stimulus and electrode configuration in the table in appendix G(a). In appendix G(b), the individual waveforms of the ABR measurements per stimulus are also shown. The effects of stimulus and electrode configuration on the ABR amplitudes were investigated by means of the Friedmann ANOVA followed by the Wilcoxon signed-ranks test.

6.6.2 Stimulus

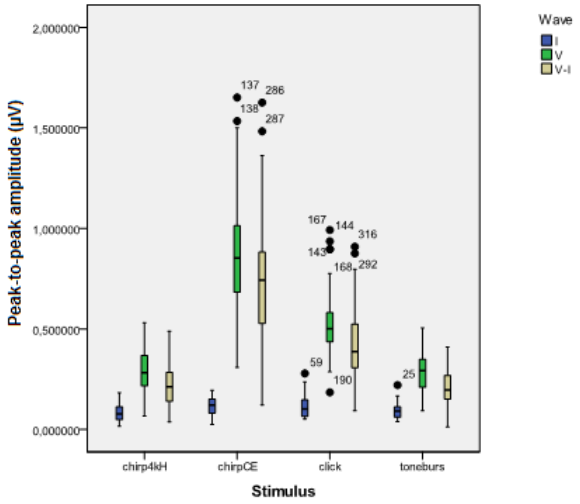

Figure 14. *Amplitudes of wave-I, wave-V and wave-V-I for the CE-chirp, the click, the narrowband 4 kHz CE-chirp and the toneburst.*

Based on the boxplot in figure 14, the order of stimuli that evoke the greatest ABR amplitudes is as follows: CE-chirp > click > narrowband CE-chirp = toneburst. The results of the Friedman's ANOVA and the Wilcoxon signed-ranks test are shown in table 9.

Table 9. *The results of the statistical analysis of the effect of stimulus on the peak-to-peak ABR amplitudes and the ABR ratio.* EC = electrode configuration, W = wave, F(df) and z = the test statistics of the Friedman's ANOVA (together with the degrees of freedom) and the Wilcoxon signed-ranks test respectively, N = number of subjects, p = the significance and *r* = the effect size.

EC	W	Friedman's ANOVA			Wilcoxon signed-ranks				
		N	F(3)	p	Paired comparison	N	z	p	*r*
CL	V	13	26.723	<0.001	CEchirp>4 kHz chirp	13	3.18	<0.001	-0.882
					Toneburst>4 kHz chirp	13	-0.105	0.932	-0.029
					Click>toneburst	13	-3.040	0.001	-0.843
					Click>4 kHz chirp	13	-2.760	0.003	-0.765
					CE chirp>click	13	-2.760	0.003	-0.765
					CEchirp>toneburst	13	-3.180	<0.001	-0.882
IL	I	10	5.880	0.120					
	V	13	35.677	<0.001	CEchirp>4 kHz chirp	13	-3.180	<0.001	-0.882
					CEchirp>toneburst	13	-3.180	<0.001	-0.882
					Click>toneburst	13	-3.180	<0.001	-0.882
					Click>4 kHz chirp	13	-3.180	<0.001	-0.882
					CE chirp>click	13	-3.180	<0.001	-0.882
					Toneburst>4 kHz chirp	13	-1.293	0.216	-0.359
	V-I	10	25.560	<0.001	CEchirp>4 kHz chirp	13	-3.180	<0.001	-0.882
					CEchirp>toneburst	12	-3.059	<0.001	-0.883
					Click>toneburst	10	-2.803	0.002	-0.886
					Click>4 kHz chirp	10	-2.701	0.004	-0.854
					CE chirp>click	10	-2.803	0.002	-0.886
					Toneburst>4 kHz chirp	12	-0.784	0.470	-0.226
	V/I	10	14.760	0.001	CEchirp>4 kHz chirp	13	-2.271	0.021	-0.630

					CEchirp>toneburst	12	-2.981	0.001	-0.861
					Click>toneburst	10	-2.599	0.006	-0.822
					Click>4 kHz chirp	10	-0.866	0.432	-0.274
					CE chirp>click	10	-1.886	0.064	-0.596
					4 kHz chirp>toneburst	12	-0.863	0.424	-0.249
IE	I	11	3.764	0.302					
	V	12	33.300	<0.001	CEchirp>4 kHz chirp	12	-3.059	<0.001	-0.883
					CEchirp>toneburst	12	-3.059	<0.001	-0.883
					Click>toneburst	13	-3.181	<0.001	-0.882
					Click>4 kHz chirp	12	-3.059	<0.001	-0.883
					CE chirp>click	12	-3.059	<0.001	-0.883
					Toneburst>4 kHz chirp	12	-0.784	0.470	-0.226
	V-I	11	26.673	<0.001	CEchirp>4 kHz chirp	12	-3.059	<0.001	-0.883
					CEchirp>toneburst	11	-2.934	0.001	-0.885
					Click>toneburst	12	-2.981	0.001	-0.861
					Click>4 kHz chirp	11	-2.845	0.002	-0.858
					CE chirp>click	11	-2.934	0.001	-0.885
					Toneburst>4 kHz chirp	11	-1.156	0.278	-0.349
	V/I	11	14.018	0.002	CEchirp>4 kHz chirp	12	-2.981	0.001	-0.861
					CEchirp>toneburst	12	-1.569	0.129	-0.453
					Click>toneburst	12	-1.726	0.092	-0.498
					Click>4 kHz chirp	11	-1.067	0.320	-0.322
					CE chirp>click	11	-2.756	0.003	-0.831
					Toneburst>4 kHz chirp	11	-0.356	0.765	-0.107

The differences between the amplitudes of the CE-chirp vs. the toneburst, the CE-chirp vs. the 4 kHz chirp, the CE-chirp vs. the click, the click vs. the toneburst and the click vs. the 4 kHz chirp were mostly significant. The wave-I amplitudes, however, did not differ significantly between stimuli. The parameter wave-V/I ratio did least reach significance for these comparisons, whereas the parameters wave-V and wave-V-I most often reached significance for these comparisons. The difference between the toneburst and the 4 kHz chirp never reached significance. All results do confirm our hypothesized hierarchy of stimuli: in most cases, the CE-chirp differred significantly from the click and the click itself evokes larger amplitudes than the 4 kHz CE-chirp. There was not found a significant difference between responses to the 4 kHz CE-chirp and the 4 kHz toneburst stimulation.

6.6.3 Electrode configuration

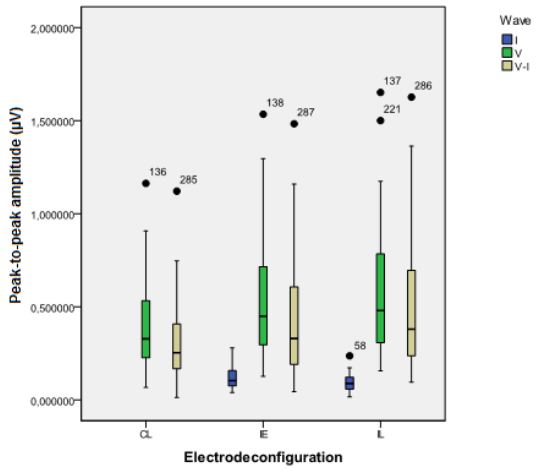

Figure 15. *Amplitudes of wave-I, wave-V and wave-V-I for the CL electrode configuration (mastoid electrode on left ear), the IE electrode configuration (TIProde in the ear canal) and the IL electrode configuration (mastoid electrode on the right ear).*

When looking at figure 15, there is not much difference between electrode configurations, although the IL setup seems to evoke rather larger wave-V amplitudes than the IE and CL set-up, with the CL configuration producing the smallest wave-V amplitudes. The wave-I amplitude tends to be a tiny bit higher using an ear canal electrode. The results of the Friedman's ANOVA and the Wilcoxon signed-ranks test indicate these findings and are shown in table 10.

Table 10. *The results of the statistical analysis of the effect of electrode configuration on the peak-to-peak ABR amplitudes and the ABR ratio.* W = wave, N = number of subjects, F(df) and z = the test statistics of the Friedman's ANOVA (together with the degrees of freedom) and the Wilcoxon signed-ranks test respectively, p = the significance and *r* = the effect size.

Stimulus	W	Friedman's ANOVA			Wilcoxon signed-ranks				
		N	F(df)	P	Paired comparison	N	z	p	*r*
Chirp 4 kHz	I	12	5.333(1)	0.039					
	V	12	8.167(2)	0.017					
CE-chirp	I	12	1.333(1)	0.388					
	V	12	16.667(2)	<0.001	IL>CL	13	-2.760	0.003	-0.765
					IE>CL	12	-2.981	0.001	-0.861
					IL>IE	12	-2.119	0.033	-0.612
Toneburst	I	12	3.000(1)	0.146					
	V	13	11.412(2)	0.002	IL>CL	13	-2.761	0.003	-0.766
					IE>CL	13	-3.061	<0.001	-0.849
					IL>IE	13	-2.343	0.016	-0.650
Click	I	10	10.000(1)	0.002	IE>IL	10	-2.803	0.002	-0.886
	V	13	18.000(2)	<0.001	IL>CL	13	-3.040	0.001	-0.843
					IE>CL	13	-3.180	<0.001	-0.882
					IL>IE	13	-2.027	0.042	-0.562

For wave-I, the differences between the electrode configurations reached significance only for the click. In this stimulus, the observed hierarchy (IE>IL) was statistically significant. For wave-V, the observed hierarchy was mostly represented in the results but differences between the IE and IL electrode configurations were not significant. For the toneburst and the 4 kHz chirp, one respectively no parameter was significantly different between electrode configurations. For the CE-chirp and the click, one respectively two parameters were significantly different between electrode configurations.

6.7 ABR and hearing questionnaire analysis

6.7.1 HQ scores

The scores on the HQ were assessed to have a relationship with any of the ABR parameters. This was done by means of bivariate correlation analysis. Scatter plots of the relation of these scores with the ABR amplitudes of all independent variables in different conditions are shown in figures 16-19. For the CE-chirp, a very small decline in wave-I amplitude can be observed the higher the measured noise exposure. For the click, the narrowband CE-chirp and the toneburst, this is not very clear. For wave-V, wave-V-I amplitude and the wave-V/I ratio, there seems to be no relationship with the score on the HQ. However, none of the correlations were significant. The correlations between scores on the HQ and the amplitudes of wave-I were not predominantly negative or positive. The correlations between the noise exposure measurement and wave-V, wave-V-I or wave-V/I amplitude were mostly negative or close to zero.

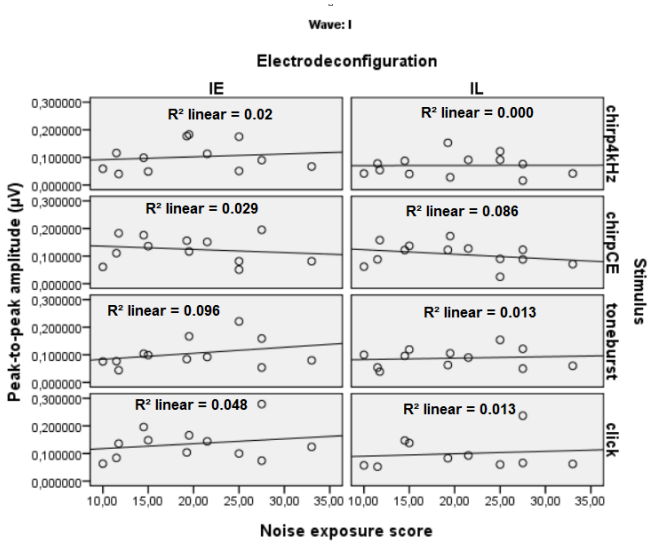

Figure 16. *Scatter plot of response amplitudes (in µV) of wave-I vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

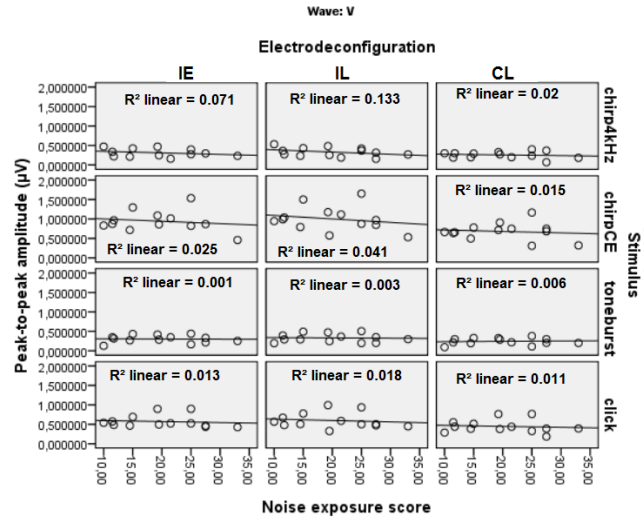

Figure 17. *Scatter plot of response amplitudes (in µV) of wave-V vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

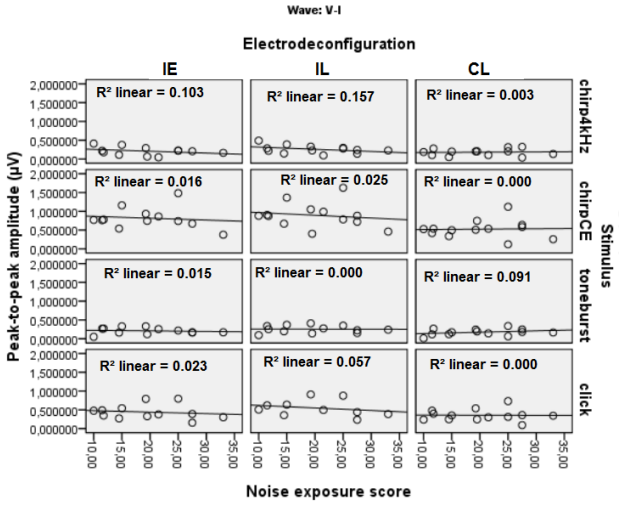

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Figure 18. *Scatter plot of response amplitudes (in µV) of wave-V-I vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

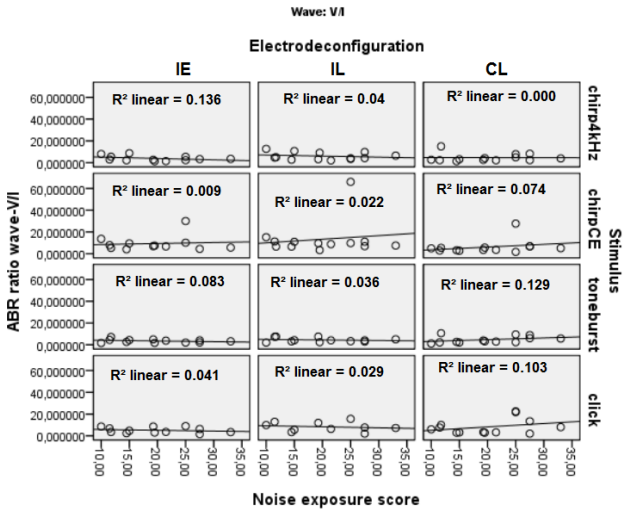


Figure 19. *Scatter plot of the ABR ratio wave-V/I vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

6.7.2 Groups based on HQ score

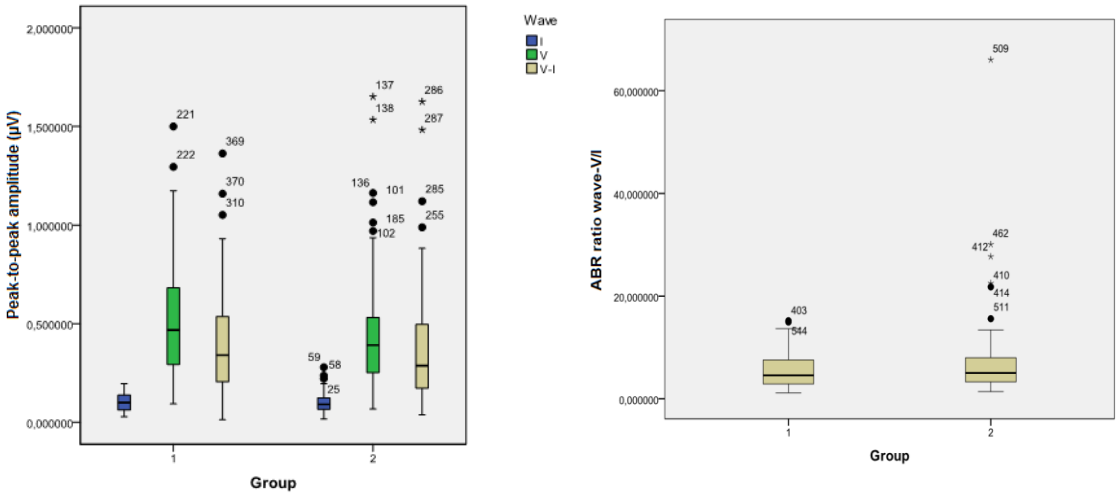


Figure 20. *ABR parameters (left: amplitudes of wave-I, wave-V and wave-V-I and right: the ABR ratio wave-V/I) for subjects with a lower amount of noise exposure (group 1) vs. subjects with a higher amount of noise exposure (group 2) for the different electrode configurations together.*

In figure 20, the amplitudes for wave-I, wave-V and wave-V-I all seem slightly smaller in persons with a higher noise exposure score, according to our HQ. The results of the Mann-Whitney U test are shown in table 11.

Table 11. *The results of the statistical analysis of the effect of noise exposure group on the peak-to-peak ABR amplitudes and the ABR ratio.* N = number of subjects, U = the test statistic of the Mann-Whitney U test, p = the significance and *r* = the effect size.

Wave	Mann-Whitney U				
	Paired comparison	N	U	p	*r*
I	Group 1>group 2	96	1080.000	0.693	-0.041
V	Group 1>group 2	154	2581.000	0.194	-0.105
V-I	Group 1>group 2	148	2445.500	0.316	-0.083
V/I	Group 2>group 1	148	2512.000	0.457	-0.061

Although amplitudes were often greater in the low noise exposure group in comparison with the high noise exposure group no significant differences in tested ABR parameters between the groups were found. Because test results were not significant, they were not further analysed by splitting data according to stimuli and electrode configurations. In appendix H, mean peak-to-peak amplitudes per wave, group, stimulus and electrode configuration are included.

6.8 ASSR

6.8.1 Global results of the noise sweep

The descriptive statistics (ranges, minima, maxima, means and SDs) of the general ASSR responses to the noise sweep are shown separately per range of modulation frequency and elec-

trode configuration in appendix I(a). The responses in the lower frequency ranges are twice as large as the amplitudes in the higher frequency ranges. The coefficient of variation (CV) was calculated (Stamper & Johnson, 2014) and shown in table 12 to assess the intersubject variability of the ASSR in different ranges and recorded by different electrode configurations, by means of the following formula: (standard deviation/mean responses in the different frequency ranges) x 100.

Table 12. *Intersubject variability (coefficient of variation) for the mean ASSR amplitudes to the noise sweep in different electrode configurations (EC).*

	Range						
EC	150-250	150-300	275-275	35-55	40-40	75-90	80-80
CL	43.478	40.910	25.000	38.298	11.864	36.957	37.255
IE	52.174	50.000	58.333	25.532	33.898	33.962	42.308
IL	55.556	54.167	28.571	37.255	33.333	48.077	36.066

The only trend that can be found in the intersubject variability of the ASSRs is that it seems to be slightly greater in higher frequency ranges compared to the lower frequency regions. In appendix I(b), the individual response amplitudes to the noise sweep are shown per electrode configuration. In all subjects there was an approximately periodical response to modulation frequencies between 35-300 Hz. To obtain an overall view of this periodicity, a grand average plot of the noise sweep is shown in figure 21. The course of the response is then described.

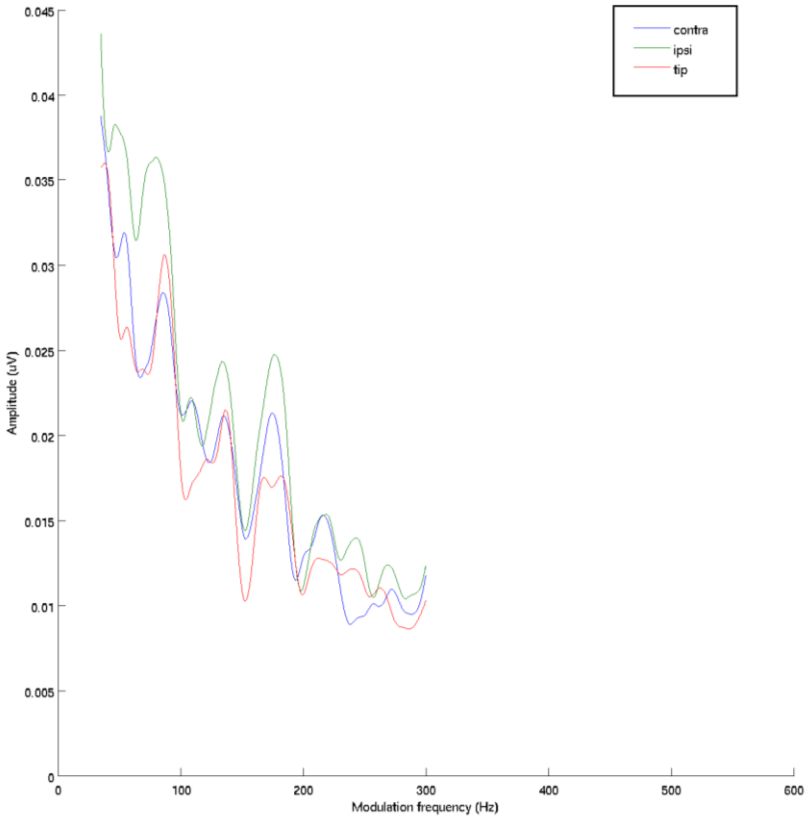


Figure 21. *Grand average ASSR spectrum in response to the noise sweep.*

At approximately 40 Hz and 80 Hz a peak in the response amplitude can be observed. Near 30 Hz and 70 Hz a response minimum is seen. This 40 Hz periodicity seems to continue in higher frequencies. Additionally, a general decrease in response amplitude with frequency can be observed. The IL electrode configuration seems to evoke the largest ASSR amplitudes. The difference between the CL and IE electrode configuration does not appear to be different. The effect of electrode configuration on the dependent variables of the ASSR was subsequently investigated by means of the Friedman's ANOVA followed by the Wilcoxon signed-ranks test.

6.8.2 Electrode configuration

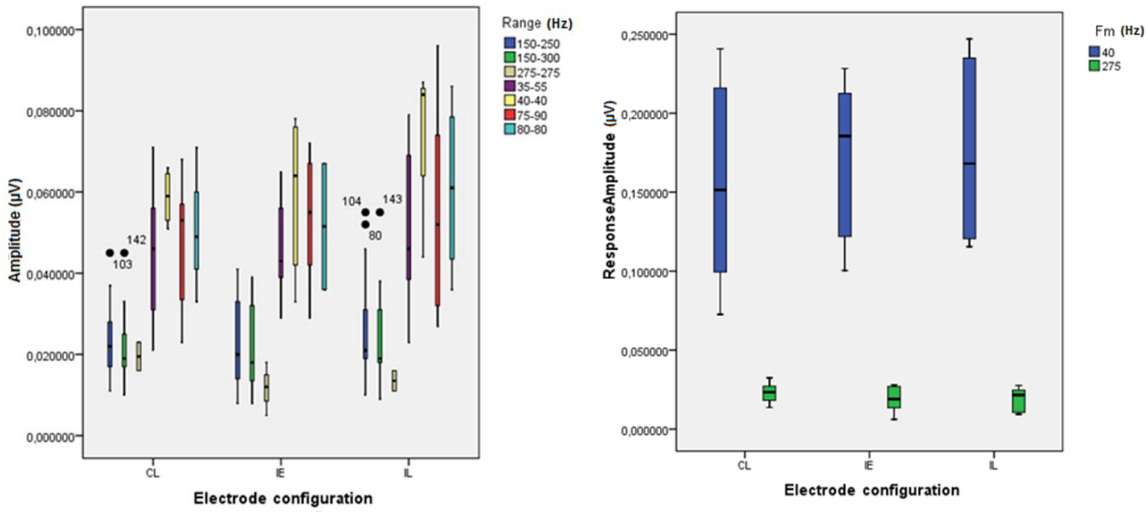


Figure 22. *ASSR parameters (left: mean amplitudes to the noise sweep in different frequency ranges and right: response amplitudes to the 40 and 275 AM noise) for the different electrode configurations.*

When looking at the left part of figure 22, there is not much difference between electrode configurations for the higher frequency ranges (150-250 Hz, 150-300 Hz and 275-275 Hz). For the lower frequency ranges (35-55 Hz, 40-40 Hz, 75-90 Hz and 80-80 Hz), the following hierarchy is found: IL>IE>CL. For the response amplitudes, a larger value is found for the often in literature described frequency ranges of 35-55 Hz, 40-40 Hz, 75-90 Hz and 80-80 Hz in comparison with the other frequency ranges, although the latter comprise a larger frequency width. The results of the Friedman's ANOVA on the amplitudes of the noise sweep are shown in table 13. Only the ranges in which the Hotteling's T^2-test yielded significant data points were included in the statistical analyses. Only a few data points in the ranges of 40-40 Hz, 80-80 Hz and 275-275 Hz were significant, although they evoked large amplitudes as can be seen in the boxplot above. However, because it is impossible to become valid results of statistical analyses on only a few data points, these ranges were omitted for further analysis.

Table 13. *The results of the statistical analysis of the effect of electrode configuration on the ASSR amplitudes.* N = number of subjects, F(df) = the F-statistic together with the degrees of freedom and p = the significance.

Range	Friedman's ANOVA		
	N	F(2)	p
35-55	6	4.261	0.136
75-90	5	1.000	0.630
150-250	12	4.043	0.135
150-300	12	5.644	0.063

The results indicate that the electrode configuration does not have a significant effect on the responses to the noise sweep. Therefore, the Wilcoxon signed-ranks test was not conducted. The response amplitudes to the 40 Hz and 275 Hz AM noise per electrode configuration are shown in the right part of figure 22. The response amplitudes to the 40 Hz ASSR are naturally far greater than the response amplitudes to the 275 Hz ASSR. Between the electrode configurations, no substantial difference can be observed. The results of the Friedman's ANOVA are shown in table 14. As results of this statistical analysis were again not significant, the Wilcoxon signed-ranks test was not conducted.

Table 14. *The results of the statistical analysis of the effect of electrode configuration on the AM noise between different electrode configurations.* N = number of subjects, F(df) = the F-statistic together with the degrees of freedom and p = the significance.

Modulation frequency	Friedman's ANOVA		
	N	F(2)	p
40 Hz	6	4.000	0.184
275 Hz	6	4.333	0.142

6.9 ASSR and hearing questionnaire analysis

6.9.1 HQ scores

The scores on the HQ were assessed to have a relationship with any of the ASSR parameters. This was done by means of bivariate correlation analysis. In this way, correlations between the scores on the questionnaire and all ASSR parameters were investigated. Scatter plots of the relation of these scores with the mean ASSR amplitude in different ranges, the ASSR ratio (150-250 Hz on 35-55 Hz) and the amplitudes to the 40 and 275 Hz AM noise for the different electrode configurations, are shown in figures 23-28 for the frequency ranges with a sufficient number of significant data points.

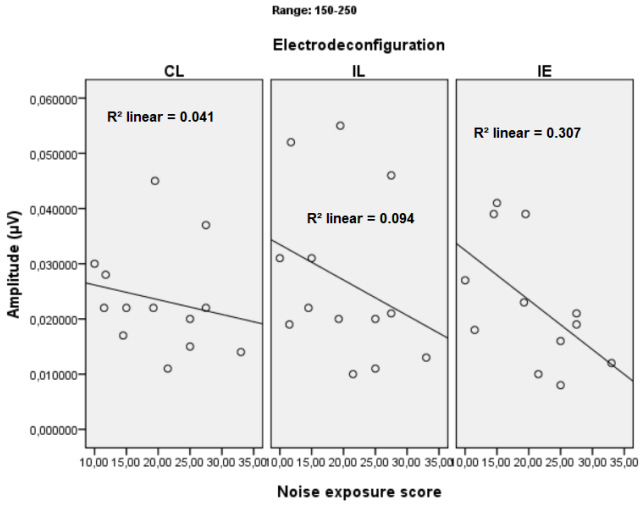


Figure 23. *Scatter plot of mean amplitude (in µV) in the range 150-250 Hz vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

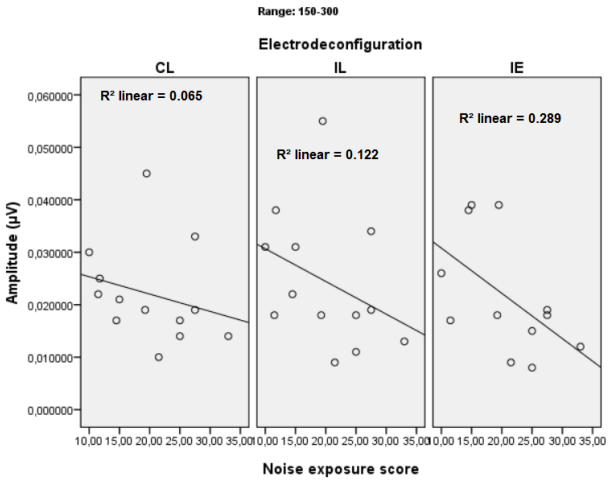


Figure 24. *Scatter plot of mean amplitude (in µV) in the range 150-300 Hz vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

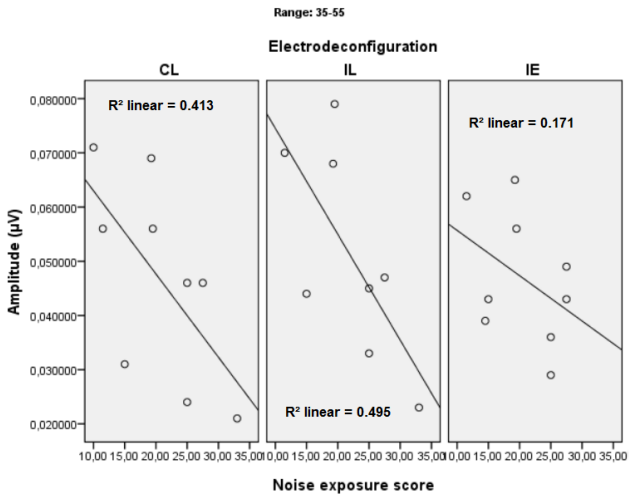


Figure 25. *Scatter plot of mean amplitude (in µV) in the range 35-55 Hz vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

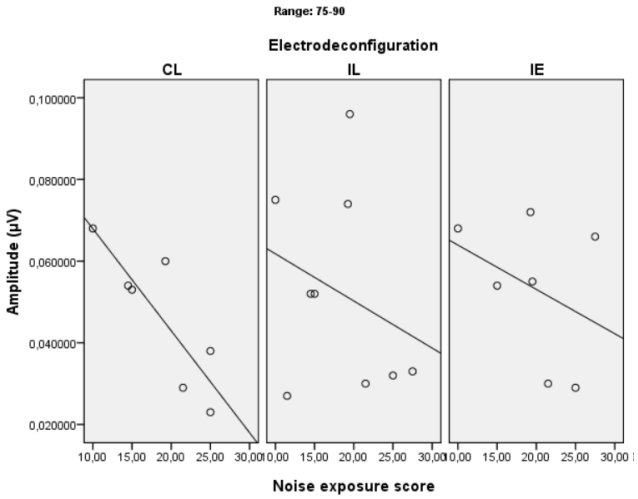


Figure 26. *Scatter plot of mean amplitude (in µV) in the range 75-90 Hz vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

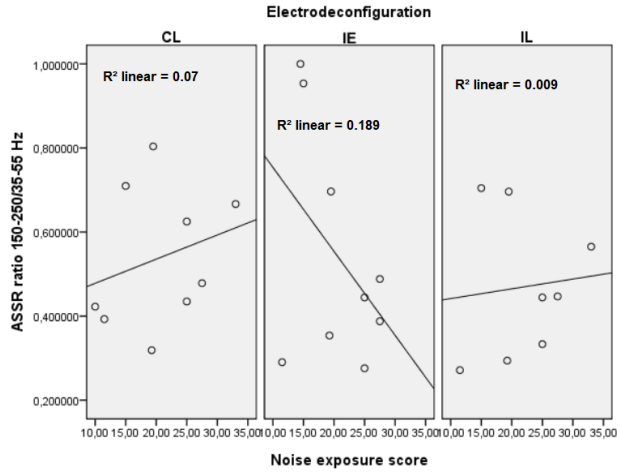


Figure 27. *Scatter plot of the ASSR ratio vs. the score on the HQ for each stimulus and electrode configuration.* The higher the score, the more exposed the subject has been to noise for the past five years.

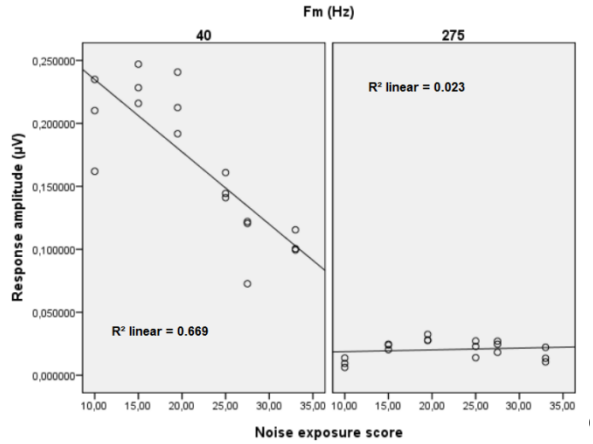


Figure 28. *Scatter plot of responses to the AM noise (40 Hz and 275 Hz) vs. the score on the HQ for all electrode configurations together.* The higher the score, the more exposed the subject has been to noise for the past five years.

Based on the figures, there seems to be a negative relationship between the scores on the HQ and the amplitudes in the ranges 150-250 Hz, 150-300 Hz, 75-90 Hz and 35-55 Hz. Also for the amplitudes to the 40 Hz AM noise, a decline with HQ score is seen. However, only for the responses to the 40 Hz AM noise in the IL electrode configuration, a significant correlation with the HQ score was found (N=6, r= -0.949, p=0.004). In the IE configuration, the correlation reached a significance of 0.011, which is near to our premised α-level of 0.01 (N=6, r= -0.913, p=0.011).

6.9.2 Groups based on HQ score

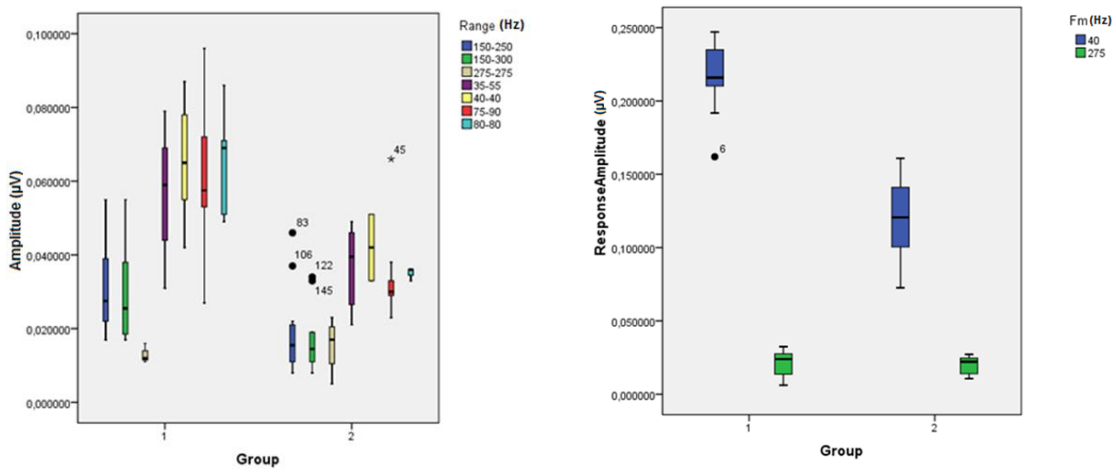


Figure 29. *ASSR parameters (left: mean amplitudes to the noise sweep in all frequency ranges and right: response amplitudes to the 40 and 275 AM noise) for subjects with a lower amount of noise exposure (group 1) vs.subjects with a higher amount of noise exposure (group 2).*

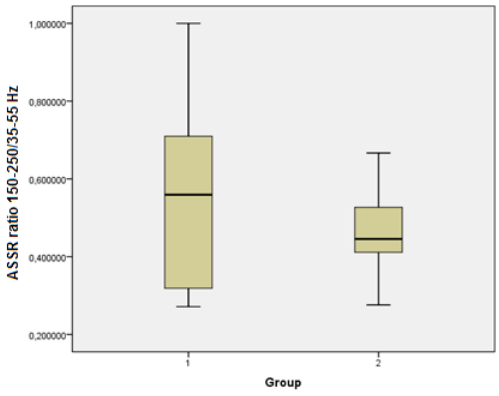


Figure 30. *The ASSR ratio for subjects with a lower amount of noise exposure (group 1) vs. subjects with a higher amount of noise exposure (group 2).*

In the left part of figure 29, the responses in all frequency ranges seem smaller in persons who have been exposed more to noise in the last five years (group 2), according to our HQ. In the right part of figure 29, the response amplitude to the 40 Hz AM noise is also clearly lower for subjects with a higher noise exposure. However, for the response amplitudes to the 275 Hz AM noise no clear difference between groups can be seen. For the ratio 150-250 Hz on 35-55 Hz,

there also seems to be a difference between the two groups in favour of the low noise exposure group based on figure 30. The results of the Mann-Whitney U test are shown in table 15.

Table 15. *The results of the statistical analysis of the effect of noise exposure group on the ASSR amplitudes to the noise sweep in different frequency ranges and the responses to the AM noise.* First, the general responses were statistically compared between groups. Second, the analyses were repeated for the responses in different frequency ranges. N = number of subjects, U = the statistic of the Mann-Whitney U test, p = the significance and *r* = the effect size.

Stimulus	Range/f_m	Mann-Whitney U				
		Paired comparison	N	U	p	*r*
Noise sweep	General	Group 1 > group 2	153	1230.000	<0.001	-0.489
	150-250	Group 1 > group 2	38	136.000	0.203	-0.209
	150-300	Group 1 > group 2	38	158.000	0.529	-0.104
	275-275	Group 1 > group 2	7	4.000	0.629	-0.267
	35-55	Group 1 > group 2	26	48.000	0.066	-0.363
	40-40	Group 1 > group 2	12	3.000	0.182	-0.4347
	75-90	Group 1 > group 2	23	60.500	0.889	-0.033
	80-80	Group 2 > group 1	9	1.500	0.060	-0.648
	(150-250) /(35-55)	Group 1 > group 2	26	73.000	0.586	-0.111
AM noise	40	Group 1 > group 2	18	0.000	<0.001	-0.843
	275	Group 1 > group 2	18	35.000	0.666	-0.115

For the noise sweep, the general mean response amplitudes were significantly smaller in the high noise exposure group (group 2) than in the low noise exposure group (group 1). When analyses were repeated after splitting data per frequency range, the significant effect disappeared. However, after splitting data per frequency range and electrode configuration (not shown in the table), it was found that the mean response amplitude for the frequency range 150-250 Hz in the IE electrode configuration was significantly different between groups (group 1>group2) (N=12, U=2.000, p=0.009, *r*= -0.741). Furthermore, the responses to the 40 Hz AM noise were significantly greater for the low noise exposure group (group 1) than the high noise exposure group (group 2). When it was assessed in which electrode configuration the effect was greatest, the significance disappeared. In appendix J, mean response amplitudes in different frequency ranges and the ASSR ratio (150-250 Hz on 35-55 Hz) to the noise sweep and mean response amplitudes to the 40 Hz and 275 Hz AM noise are included, per group and electrode configuration.

6.10 ABR vs. ASSR analysis

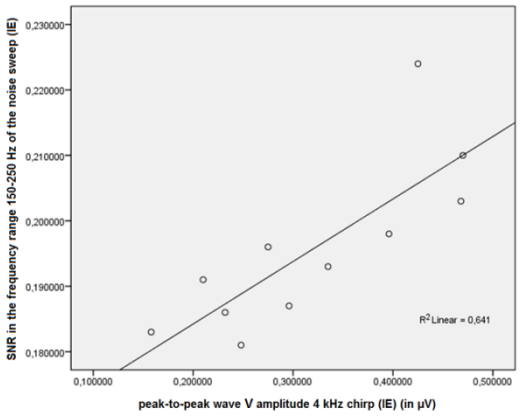
All parameters of the ABR were assessed to have correlations with the ASSR parameters, by means of bivariate correlation analysis. All significant correlations ($\alpha<0.01$) are summarized in table 16. The following parameters were included in the analysis. For ABR: wave-I, wave-V and

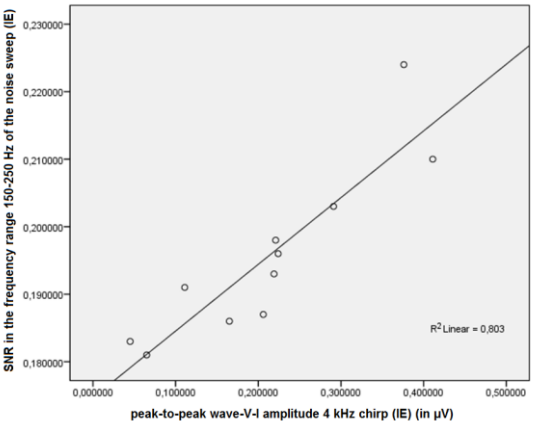
wave-V-I peak-to-peak amplitudes and the wave-V/I ratio for the ABR analysed in the frequency domain and (biased and unbiased) response amplitudes for the ABR analysed in the time domain. For ASSR: mean response amplitudes and SNRs to the noise sweep in the frequency ranges of 35-55 Hz, 40-40 Hz, 75-90 Hz, 80-80 Hz, 150-250 Hz, 150-300 Hz and 275-275 Hz; response amplitudes to the 40 Hz and 275 Hz AM noise and the magnitude of the ratio of the mean response amplitudes in the range 150-250 Hz on 35-55 Hz.

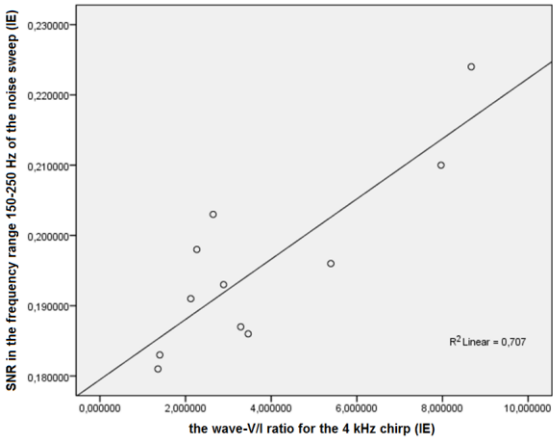
Table 16. *Correlations (r) between ABR and ASSR parameters, exact significances (p) and number of subjects (N) per pair of parameters.* As to the codes: stim. = stimulus, W = wave, EC = electrode configuration, U = unit, f_m = modulation frequentie, ptp A = peak-to-peak amplitude in µV, NS = noise sweep, SNR = the mean signal-to-noise ratio in the frequency range (which is indicated in the table) in µV, A = the mean amplitude in the frequency range (which is indicated in the table) in µV, B A = biased response amplitude for the short-duration signals as analysed in the time domain in µV, UB A = unbiased response amplitude for the short-duration signals as analysed in the time domain in µV. For the latter two dependent variables, no difference in waves can be made (indicated by '/').

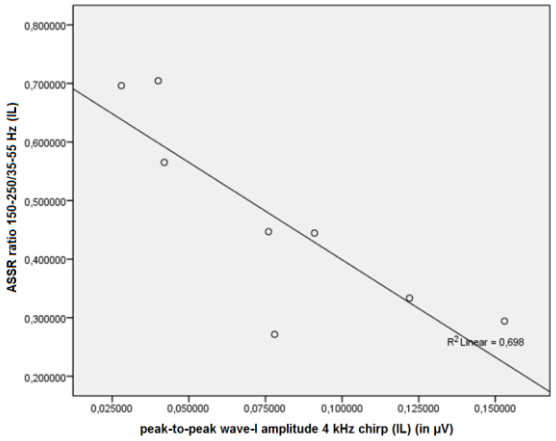
ABR parameter				ASSR parameter				r	p	N
Stim.	W	EC	U	Stim.	Range/f_m(Hz)	EC	U			
4kHz chirp	V	IE	ptp A	NS	150-250	IE	SNR	0.801	0.003	11
4kHz chirp	V-I	IE	ptp A	NS	150-250	IE	SNR	0.896	<0.001	11
4kHz chirp	V/I	IE	ptp A	NS	150-250	IE	SNR	0.841	0.001	11
4kHz chirp	I	IL	ptp A	NS	(150-250)/ (35-55)	IL	/	-0.836	0.010	8
4kHz chirp	V/I	IL	ptp A	NS	(150-250)/ (35-55)	IL	/	0.909	0.002	8
Click	/	CL	UB A	NS	150-250	CL	A	0.889	<0.001	11
Click	/	CL	UB A	NS	150-300	CL	A	0.864	0.001	11
4kHz chirp	/	CL	B A	NS	150-300	IL	A	0.698	0.008	13
4kHz chirp	/	CL	UB A	NS	150-250	CL	A	0.858	0.001	10
4kHz chirp	/	CL	UB A	NS	150-300	CL	A	0.852	0.002	10

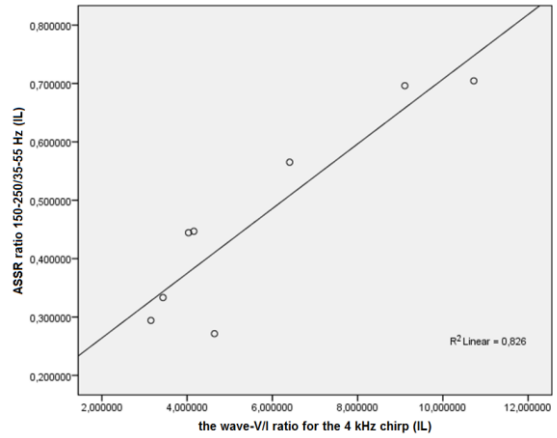
Significant correlations due to a distortion by one data point were not included in the table. Only one significant correlation with the ABR wave-I was found (with the ASSR ratio). The other significant relations were found for ABR wave-V-I and wave-V/I and for the ABR analysed in the frequency domain. For the ASSR parameters, all significant correlations were found with the responses in the high frequency ranges or the ASSR ratio. There was no prominence of an electrode configuration. However, for the stimuli, the 4 kHz chirp seemed to be the most sensitive to demonstrate significant correlations with the ASSR parameters. The scatter plots of all these significant correlations are shown in figure 31.

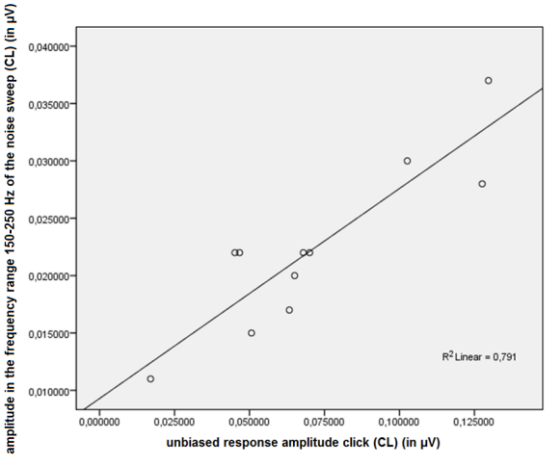

SNR in the frequency range 150-250 Hz of the noise sweep (IE)
0,230000
0,220000
0,210000
0,200000
0,190000
0,180000
R² Linear = 0,641
0,100000
0,200000
0,300000
0,400000
0,500000
peak-to-peak wave V amplitude 4 kHz chirp (IE) (in µV)


SNR in the frequency range 150-250 Hz of the noise sweep (IE)
0,230000
0,220000
0,210000
0,200000
0,190000
0,180000
R² Linear = 0,803
0,000000
0,100000
0,200000
0,300000
0,400000
0,500000
peak-to-peak wave-V-I amplitude 4 kHz chirp (IE) (in µV)


SNR in the frequency range 150-250 Hz of the noise sweep (IE)
0,230000
0,220000
0,210000
0,200000
0,190000
0,180000
R² Linear = 0,707
0,000000
2,000000
4,000000
6,000000
8,000000
10,000000
the wave-V/I ratio for the 4 kHz chirp (IE)


ASSR ratio 150-250/35-55 Hz (IL)
0,800000
0,700000
0,600000
0,500000
0,400000
0,300000
0,200000
R² Linear = 0,698
0,025000
0,050000
0,075000
0,100000
0,125000
0,150000
peak-to-peak wave-I amplitude 4 kHz chirp (IL) (in µV)


ASSR ratio 150-250/35-55 Hz (IL)
0,800000
0,700000
0,600000
0,500000
0,400000
0,300000
0,200000
R² Linear = 0,826
2,000000
4,000000
6,000000
8,000000
10,000000
12,000000
the wave-V/I ratio for the 4 kHz chirp (IL)


amplitude in the frequency range 150-250 Hz of the noise sweep (CL) (in µV)
0,040000
0,035000
0,030000
0,025000
0,020000
0,015000
0,010000
R² Linear = 0,791
0,000000
0,025000
0,050000
0,075000
0,100000
0,125000
unbiased response amplitude click (CL) (in µV)

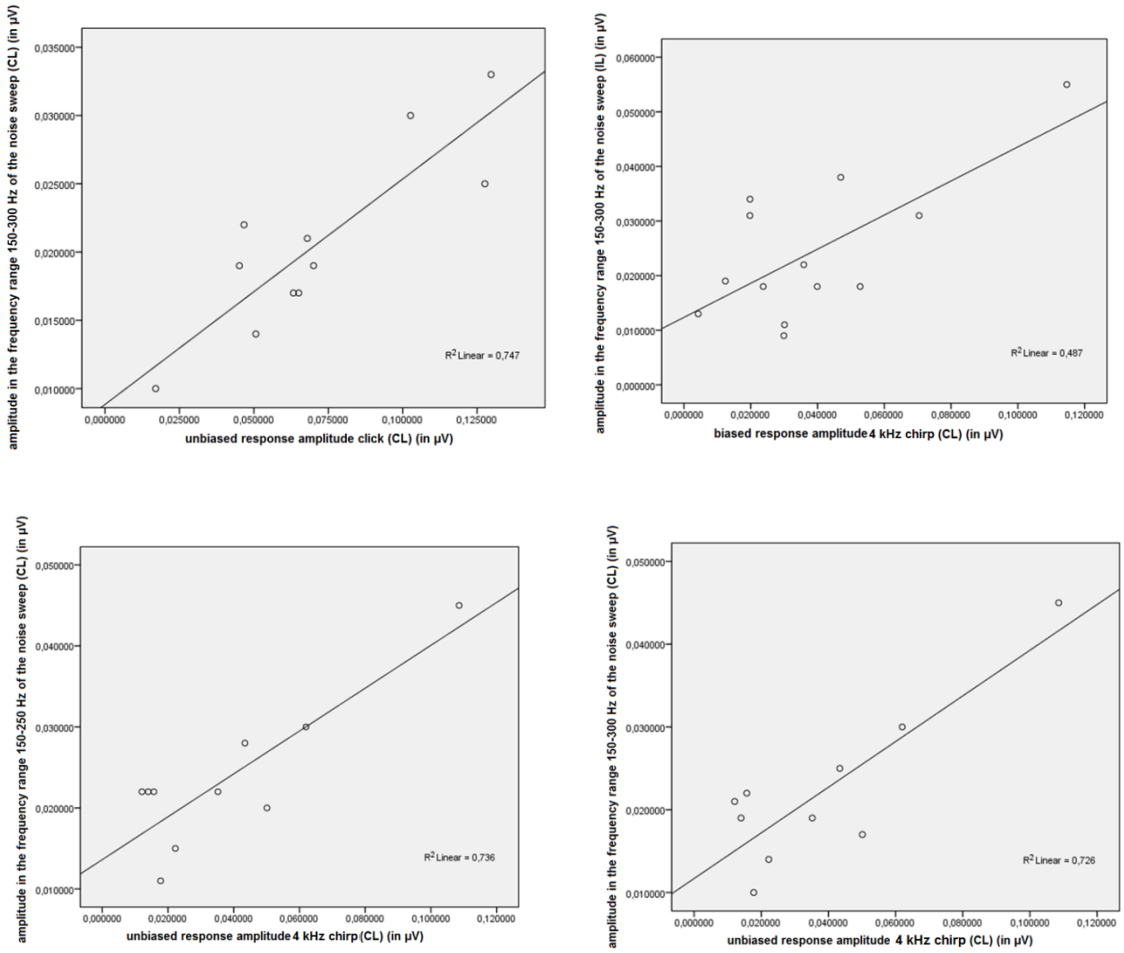


Figure 31. *Scatter plots of all significant correlations between ABR and ASSR parameters*. The value of R^2 is shown in the right lower corner.

6.11 Summary of the results

In this chapter, all the results of the analyses that were carried out were presented. In summary the following important results were found. The SRTs did not differ significantly between the two groups, whereas the 4 kHz pure tone threshold did. For the ABR analysis, the CE-chirp evoked larger amplitudes than the click, and no differences were obtained between the 4 kHz chirp and the toneburst. For wave-V, the IL electrode configuration and the IE configuration measured larger responses than the CL configuration. For wave-I, the IE configuration measured larger responses than the IL configuration in the click. Between the ABR parameters and the noise exposure scores respectively the groups based on these scores existed no significant correlations respectively differences. For the ASSR analysis, there were no significant differences between electrode configurations for all dependent variables. There was found a significant correlation between the responses to the 40 Hz AM noise ASSR and the HQ scores (IL and IE). Between the two groups based on the HQ scores, smaller response amplitudes to the noise sweep were found for the high noise exposure group in general and more specifically in the

range 150-250 Hz (IE). Also, the responses to the 40 Hz AM noise ASSR were greater for the low noise exposure group in comparison with the high noise exposure group. For the ABR vs. ASSR analysis, significant correlations were found between all parameters (wave I, wave V, wave-V-I, wave-V/I) of the 4 kHz chirp and ASSRs in high frequency ranges, but did not follow our expectations.

Chapter 7: Discussion

7.1 Introduction

The first question that will be answered in this section is if noise exposure has caused measurable damage to inner ears of NH subjects who have had a considerable experience in noisy conditions. The second question that will be answered is if and how ASSR and ABR are related.

7.2 Threshold measurements

As the term '*hidden* hearing loss' suggests, this kind of HL is not easily found using the standard audiometric measures, e.g. pure tone audiometry, because it does not affect the hearing thresholds (Stamper & Johnson, 2014). In this study, none of the participants demonstrated a deviation from NH thresholds (>20 dB HL) and no significant correlation was found between the 4 kHz threshold and the HQ ($F(1,11)=0.966$, $r=0.284$, $p=0.347$), indicating the noise exposure score does not increase significantly with higher thresholds at the frequency of 4 kHz, which are first affected by noise exposure. However, in 7.5 it will be clear this finding should be nuanced. As to the threshold measurements of the short duration signals, in table 17, the mean thresholds of the 13 subjects and the used dB peRETSPL calibration values (see 5.6.2) are compared.

Table 17. *Mean thresholds and dB peRETSPL values for the short-duration stimuli.*

Stimulus	Mean threshold (in dB p-peSPL)	dB peRETSPL value (in dB p-peSPL)
4 kHz toneburst	25,76923	26
100 µs click	35,76923077	33,6
CE-chirp	34,61538	32
4 kHz chirp	27,08333333	35

Except for the 4 kHz chirp, our data closely approximated the average peRETSPL values from literature. The peRETSPL value for this stimulus was based on a lower repetition rate than was used in this study (40 Hz). The general trend is a lowering of peRETSPL values with increasing

stimulus rate (approximately 3 dB/70 Hz) (Gøtsche-Rasmussen et al., 2012). However, this cannot entirely explain the difference (maximum one or two dB) we have obtained between the peRETSPL value found in literature and found in our study. Because we had only 13 subjects, the image that is obtained for the zero dB nHL value of the 4 kHz chirp can be distorted, as some subjects had thresholds of 30 and 35 dB p-peSPL (see appendix E). However, more subjects had lower thresholds, e.g. 25 dB p-peSPL.

7.3 Hearing questionnaire

Stamper & Johnson (2014), which also tried to detect HHL in humans, demonstrated with their HQ that the influence of music listening was the main cause of a worse score on their HQ. In our study, the majority of questions ask about subjects' recreational noise exposure background, because most volunteers were young non-working adults not yet exposed to occupational noise. Having in mind the finding of Stamper & Johnson (2014), this seemed no wrong choice. In appendix C, it is described based on which studies our HQ was constructed. Other elements that could have been included are the following. An important element demonstrated by Feder et al. (2013) is the fact that subjects who created a tighter fit between their ear and the earphone listened to louder music and this would thus have been an important risk factor to include. Also, Niskar et al. (2001) stated that the use of a portable audio player in noisy environments (e.g. public transportation) would cause the person to turn up the volume to overpower the environmental sound and thus be at greater risk for (hidden) HL. In our study, the number of different locations where subjects listened to their portable audio player was taken into account, but not the type, while this could have been a more sensitive measurement.

Furthermore, because we wanted to optimally adjust the HQ to the needs of our research, we created a new HQ. Consequently, the HQ and the scoring is not standardized nor validated. In literature concerning recreational noise exposure or HHL in humans, questionnaires and their scoring are frequently standardized and validated (e.g. Stamper & Johnson, 2014). Therefore, the self made questionnaire can be a disadvantage in this study. Another disadvantage of self-report questionnaires in general, is an inadequate recall accuracy and recall bias (Coughlin, 1990). Because our HQ questioned the noise exposure in the last five years, it can be difficult for subjects to accurately remember all events in which they were exposed to noise. In several questionnaires, only one year is questioned. However, this can also be disadvantageous, since it does not accurately represents a lifetime. Furthermore, the subjects can tend to more positive answers knowing the nature of the study.

7.4 Digit triplet test

Weisz et al. (2006) suggested subjects suffering from HHL can have increased SRTs in background noise, since the neuronal loss is selective for low-SR fibers that are more resistant to masking by background noise (Costalupes et al., 1984). Furman et al. (2013) state this loss could therefore have consequences for hearing in noisy environments. To assess the subjects' hearing in these environments in this study, the DTT was conducted. The scores on this test varied between -10.091 and -13 dB SNR. Since the accuracy of the test is 0.8 dB (Jansen et al., 2013), there is a substantial difference between subjects in our study. Therefore, it was tested whether the SRTs varied with the HQ score, but no such relation was found. Additionally, it was assessed whether the SRTs differed between noise exposure groups, but again no significant differences were found, although a higher SRT value would be expected in the high noise exposure group or in subjects with a higher noise exposure score.

7.5 Detecting confounding variables

As in the study of Stamper & Johnson (2014) multiple regression analysis were carried out on the amplitudes of wave-I to assess whether behavioural threshold variation to the same stimuli used to evoke this wave could have been a contributing factor. However, no significant contributions of the thresholds to the short duration signals to wave-I amplitude were found. In this way, the hypothesis that threshold variation to the ABR stimuli is a confounding variable in the ABR measurements, can be rejected. Importantly, in figure 13 it seems that the pure tone thresholds are higher in subjects in the high noise exposure group compared to subjects in the low noise exposure group. After statistical analysis, the 4 kHz pure tone threshold differed significantly at a significance level of 0.05 (but not at the used 0.01 α-level) with lower thresholds in the group with a higher noise exposure (the difference of the mean dB HL between groups is around 9 dB HL). This study attempted to include subjects with and without potential HHL, which does not affect the thresholds of hearing. In later stages, this HL evolves to NIHL, which is first manifest in the audiogram as a dip at frequencies at and around 4 kHz (Attias et al., 2014). Thus, it seems that in the high noise exposure group in our study the HHL had already affected the audiogram within normal ranges. Therefore, the stimuli to evoke the AEP could have been presented at different sensation levels for both groups. This could have distorted other significant findings, because when stimuli are presented at lower sensation levels in the high noise exposure group, smaller response amplitudes can be attributed to the higher pure tone thresholds (due to NIHL), and not to HHL. However, since there were no significant

differences in thresholds to the short duration signals presented at 4 kHz between both groups, the correlation between the 4 kHz pure tone threshold and the noise exposure score was not significant (see 7.2) and the results of the multiple linear regression analysis in mind, this finding could be coincidal since the sample size of this study is very small. However, all results should be interpreted with this finding in mind.

7.6 ABR

7.6.1 General results

In appendix K, obtained values for the ABR amplitudes from the literature to the short duration signals are listed. In this way, they can be compared with our results. It was tried to obtain values for wave-I and wave-V for the 4 kHz toneburst, click, CE-chirp and narrowband 4 kHz CE-chirp, presented with the same parameters as in this study. However, rarely amplitudes to the exact same stimuli and stimulus parameters were found. Therefore, an average of amplitudes was made over different studies using approximately the same type of stimulus. The means and standard deviations of this averaging operation and the comparison with our data are listed in table 18.

Table 18. *Comparison of mean wave-I and wave-V amplitude between the literature and data of this study.* Means are obtained by averaging the values listed in appendix K, per stimulus and per wave.

Stimulus	Mean wave-I literature in µV (sd)	Mean wave-I current data in µV (sd)	Mean wave-V literature (sd)	Mean wave-V current data (sd)
4 kHz toneburst	0,506 (0,225)	0,083 (0,042)	0,477 (0,123)	0,293 (0,103)
100µs click	0,461 (0,173)	0,107 (0,065)	0,390 (0,107)	0,538 (0,183)
CE-chirp	/	0,118 (0,047)	0,579 (0,127)	0,872 (0,303)
NB CE-chirp	/	/	/	/

The wave-I amplitude of the toneburst and the click is substantially larger in literature, but averages were only made over values which were obtained at levels around 80-85 dB nHL or 60-75 dB sensation level (dB SL) for the toneburst and at slower rates, which makes data hard to compare. However, at higher levels and slower rates, responses grow larger (Picton et al., 2003). For the narrowband CE-chirp, no ABR amplitudes in adults were found in literature. These stimuli are relatively new and therefore not yet frequently used. Although objective threshold measurements in children are described with these narrowband chirps (e.g. Venail et al., 2014), since they are frequency specific and compensate for the traveling wave delay and therefore could be advantageous compared to the toneburst (see 3.4.1.4), supra-threshold ABR measurements in adults were not encountered. Also for the CE-chirp, no ABR

wave-I values were found in literature, since ABR wave-V is better visible. The variability in wave-I amplitude does not seem to differ substantially between our data and the data in the literature.

For wave-V amplitude, our data and the data in the literature agree better. However, in this study, amplitudes to the CE-chirp are larger and this could be due to the adjustment of the frequency spectrum to compensate for the ER-3A earphone, which was not done in literature. Variability is also greater and this could be due to the small sample size in our study. For the click, data of our study are again larger. It is not very clear why this difference is obtained, as the rate in the literature is often lower and thus larger response amplitudes would be expected.

7.6.2 Stimulus

The following explanations can be given for the obtained order of stimuli evoking the greatest amplitude. Both broadband stimuli evoke greater amplitudes than the smallband stimuli as they excite a wider range on the BM (Pinto & Matas, 2007). Additionally, the CE-chirp has been designed to activate the fibers in this range simultaneously (Wegner & Dau, 2002). The smallband chirp and the toneburst thus activate a smaller region on the BM around 4 kHz, which was the frequency of stimulation in this study. Normally, a greater amplitude to the narrowband CE-chirp than to the toneburst would be expected, because the first causes a more synchronal activation on the BM due to the delay compensation. Furthermore, the narrowband CE-chirp has a wider bandwidth than the toneburst (Gøtsche-Rasmussen et al., 2012). Therefore, a larger response is produced due to the activation over a greater area of the BM (Ferm et al., 2013). This finding was not reflected in our results. This could be due to a lack of power, which impedes in the present variability a difference to be seen, that could be seen with a larger sample size.

Besides, in the study of Rodrigues et al. (2013) in young infants, the advantage of the narrowband CE-chirp above the toneburst disappeared starting from 60 dB nHL due to upward spread of excitation (see 3.4.1.2). The non-significant difference between the narrowband CE-chirp and the toneburst in our study could also be due to this. In literature, the phenomenon of upward spread of excitation is known. Level-specific chirps, that become progressively longer the lower the stimulus level and in this way compensate for the upward spread of excitation, are demonstrated to be more efficient than the CE-chirp at high (>60 dB nHL) stimulation levels

(Elberling et al, 2010; Kristensen & Elberling, 2012). In our study, the CE-chirp was chosen, because this stimulus was demonstrated to be equally efficient than the level-specific chirp at and around 50 dB nHL (Kristensen & Elberling, 2012). Additionally, Wegner & Dau (2002) found no significant difference between chirp and click stimulation when only one-octave wide frequency regions are investigated. They explained the better synchronization of action potentials the chirp causes, does not produce an advantage when only small areas on the BM contribute to the response (one octave or less). This could also be a reason for the non-significant difference between narrowband CE-chirp and toneburst stimulation, although Ferm et al. (2013) and Rodrigues et al. (2013) did find significant differences at levels below 60 dB nHL between toneburst and narrowband CE-chirp stimulation, in favour of the last.

Differences between stimuli in the amplitudes of wave-I were not significant, whereas for wave-V this was the case for all stimuli and electrode configurations, except for the difference between the toneburst and the 4 kHz chirp (see above). The order of the stimuli evoking the greatest wave-I amplitudes, however, was the same, but the differences were probably not large enough to become significant. Thus, we can conclude wave-V amplitude is the most robust parameter to demonstrate differences. This is probably why ABR wave-V amplitude is commonly referred to in ABR literature (e.g. Kirstensen & Elberling, 2012). When comparing the wave-V-I and wave-V/I parameters, in the wave-V/I parameter the differences between stimuli were often not significant, whereas differences in evoked amplitude between stimuli were significant for wave-V-I in the IL and IE electrode configurations, except for the narrowband CE-chirp vs. the toneburst. Assuming the stimuli have the same multiplicative effect on wave-V and wave-I, the ratio does not change. In the wave-V-I parameter, the same assumption can be made but subtraction of both waves does yield a number that enables comparison between stimuli.

7.6.3 Electrode configuration

In the ABR measurements, comparisons were also made between the mastoid electrodes (IL and CL) and the ear canal electrode (IE), to answer the question which electrode placement is the better one to obtain the greatest amplitudes. For wave-I, it was found for the click that the ear canal electrode (the TIPtrode) provided the greatest amplitudes, followed by the IL mastoid electrode. For wave-V, the IL mastoid electrode measured the greatest responses, followed by the ear canal electrode, although these differences were not significant. This finding is approximately in agreement with the studies of Bauch & Olsen (1990), Stamper & Johnson (2014), Yanz & Dodds (1985), and Zhang (2010). These studies demonstrated that electrode

placement closest to the neural origin of the response leads to the best measurement of the responses. This means that for wave-I, the electrode should be as close as possible to the AN, and thus the IE configuration is the best choice. For wave-V, the mastoid should be chosen because it is more proximate to the auditory brainstem (Zhang, 2010). Both mastoids should be an adequate recording site, as wave-V can be equally measured on the left and right hemisphere, because auditory processing is bilateral from where the pathways cross. The right cochlear nucleus in the brainstem projects the auditory information to the right as well as the left superior olivary complex and thus information is processed bilaterally as early as the brainstem (Bear et al., 2007). Thus, our results join the literature except for the latter remark, since for wave-V the ipsilateral electrode measures significant greater amplitudes than the contralateral electrode. However, Bauch & Olsen (1990) and Yanz & Dodds (1985) only demonstrated these effects at high levels. Yanz & Dodds (1985) even found no more significant effects at and below 60 dB nHL. In this study, where measurements were done at 50 dB nHL, differences between electrode configurations were sometimes too small to reach significance.

Because in this study the IE electrode was advantageous over the mastoid electrode only for the wave-I of the click, it does not convincingly demonstrate the advantage of the ear canal electrode when recording wave-I commonly referred to In literature (e.g. Bauch & Olsen, 1990). Besides, it has to be considered that an IE electrode like the TIPtrode is more expensive and less practical than a conventional mastoid electrode. Furthermore, it logically seems that the broadband stimuli are more efficient to detect differences in amplitude between the electrode configurations, since they activate a broader area on the BM.

Based on the study of Stamper & Johnson (2014), the coefficient of variation was calculated for wave-I and wave-V amplitudes in the different electrode configurations to compare the variability in responses (table 19). The coefficient was calculated as follows: (SD/mean amplitude) x100. In their study a larger variability in wave-I amplitudes recorded with a tympanic membrane electrode was obtained. In our study, as in the study of Yanz & Dodds (1985), no consistent difference in the coefficient of variation for wave-I between the IE and the IL recording sites was found. However, this could be due to the small sample size in this study. For wave-V, there also seemed to be no substantial difference between recording sites. An outstanding element is that for the click the variability seems to be smaller in the IE configuration.

Table 19. *Intersubject variability (coefficient of variation) for the ABR amplitudes to different stimuli and electrode configurations (EC).*

		Stimuli			
Wave	EC	4kHz chirp	CE-chirp	Click	Toneburst
I	IE	50.980	39.200	44.444	49.524
	IL	54.930	38.318	59.000	39.773
V	CL	35.294	33.137	37.584	34.980
	IE	34.405	29.131	28.021	32.237
	IL	34.650	31.700	32.776	33.133

7.7 ABR and hearing questionnaire analysis

7.7.1 HQ scores

Several studies (e.g. Kujawa & Liberman, 2009) demonstrated that the supra-threshold ABR wave-I amplitude in mice and guinea pigs after being induced with HHL, was permanently decreased in the basal half of the cochlea. Stamper & Johnson (2014) demonstrated a similar decrease in supra-threshold ABR wave-I amplitude with greater noise exposure history in humans. Based on this, we would thus expect negative correlations between ABR wave-I amplitudes and the scores on the questionnaire, because the higher the score, the more noise-exposed the subject has been. Figure 16 showed, for the CE-chirp, a very small decrease in wave-I amplitude when the noise exposure background became higher. For the click, the narrowband CE-chirp and the toneburst, we did not see the same. Thus, the CE-chirp shows the clearest connections with the scores on the HQ. Because this stimulus measures a larger frequency range of the auditory pathway than narrowband stimuli, the responses to this stimulus would rather represent a loss of neural fibers of the AN. The narrowband CE-chirp and the toneburst only measure a small area and therefore, they represent less well the possible HHL, even though these stimuli embrace the area that is first affected by noise exposure (around 4 kHz). Besides, the more clear relation between the CE chirp and the HQ scores could also be due to larger response amplitudes (and thus a more advantageous SNR) evoked by this stimulus in comparison with narrowband stimuli and the click. However, no significant correlations between all parameters and the scores on the HQ were found after conducting bivariate correlation analysis. We hypothesize the non-significance of the results is due to the small number of subjects used in our study.

For wave-V and wave-V-I amplitude and the wave-V/I ratio, there seemed to be no relationship with the scores on the HQ. Wave-V amplitude should, due to the homeostatic mechanisms normalizing activity in the central auditory system (Schaette & McAlpine, 2011), be similar across subjects and thus not be correlated with the noise exposure scores. Indeed, correla-

tions between the HQ scores and wave-V amplitude were not significant. They were mainly negative, but often close to zero. The correlations between wave-V-I amplitude or the wave-V/I ratio and scores were again not significant, while we expected this to be positively correlated because the ratio is shown in literature to increase in subjects with HHL (Schaette & McAlpine, 2011). The correlations were also often close to zero. This means that the decrease in wave-I amplitude was not large enough to magnify this parameter.

7.7.2 Groups based on HQ score

All subjects were divided into two groups to gain greater statistical power compared to the correlation analysis, conducted in the previous section. However, no significant differences between groups were found. Thus, we can question the first hypothesis of this study: people who have been more exposed to noise have lower ABR wave-I amplitudes, equal wave-V amplitudes (as non-exposed subjects), greater wave-V-I amplitudes and a greater wave-V/I ratio.

7.8 ASSR

7.8.1 Global results of the sweep

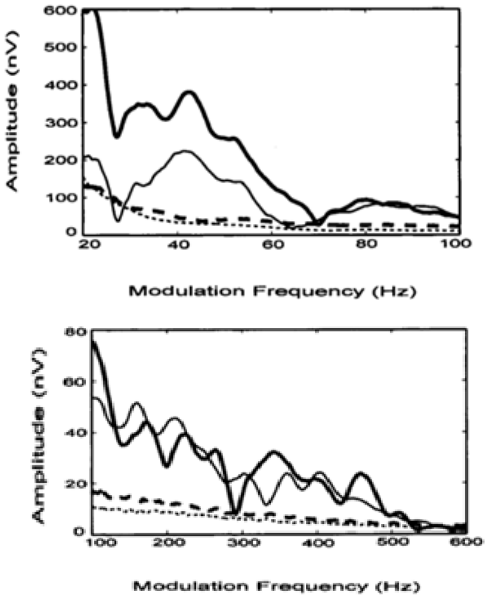


Figure 32. *The effect of stimulus repetition rate/modulation frequency on ASSR amplitude*. This figure shows the response of one subject during waking (thick line) and sleeping (tin line) to a range of modulation frequencies of 20-100 Hz (above) and 100-600 Hz (below). The stimulus is 25% AM white noise presented at 60 dB SPL. The dashed lines are the noise estimates at the response frequency. Adopted from Purcell et al. (2004).

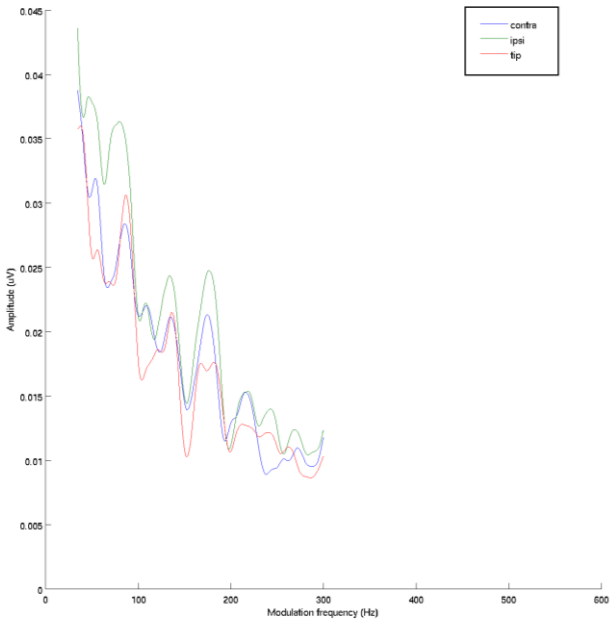


Figure 33. *Grand average ASSR spectrum in response to the noise sweep.*

In the figures 32 and 33 above, our responses to the noise sweep used in our study (50 dB nHL, f_m 35-300 Hz, 100% modulation depth) are compared to the responses to the noise sweep in the study of Purcell et al. (2004) (60 dB SPL, f_m 100-600 Hz, 25% modulation depth), whereupon our sweep stimulus was based. The thick line on the figure of Purcell et al. (2004) demonstrates the responses from one awake individual and this line is therefore compared to the grand-average response of waking subjects to the sweep used in our study. First of all, the response amplitude decreases with increasing modulation frequency, as commonly referred to in literature (e.g. Picton et al., 2003). This decrease in amplitude could represent the effect of neural adaptation, which grows larger the higher the stimulus rate (Elberling et al., 2007). As in the study of Purcell et al. (2004), a peak in the response amplitude at 40 Hz and 80 Hz is seen (which was expected from the extensive literature around these responses; e.g. Picton et al., 2003) and response minima are obtained for frequencies near 30 and 70 Hz. Galambos et al. (1981) attributed the greater ASSR amplitude to stimuli at a rate of 40 Hz to the superimposi-

tion of the peaks of the transient middle latency responses. The middle latency responses occur with interpeak intervals of 25 ms and therefore, the successive responses will be in phase when a stimulus is presented at 40 Hz (when a response is elicited every 25 ms) and superposition is thus most effective. Besides, it was suggested by Lins et al. (1995) that the 80 Hz response (when a response is generated every 12.5 ms) might represent the superimposition of wave-V of the ABR evoked by each increase in amplitude of the stimulus. Thus, our results demonstrate the same trend as this stimulus of Purcell et al. (2004).

However, Purcell et al. (2004) found significant responses until 500 Hz. In our study, however, in the pilot phase a sweep with modulation frequencies from 70-600 Hz was presented to the subjects, but because the responses to the higher frequencies (>300 Hz) were not significant, these frequencies were omitted from the stimulus in the second testing phase. In addition, response amplitudes are substantially smaller to the noise sweep used in this study than the sweep used in the study of Purcell et al. (2004). This could be the consequence of measurements at higher stimulus levels than in our study (60 dB SPL vs. 50 dB A). Therefore, the SNR is less favourable and the response amplitude can be overwhelmed by the noise in the measurement. Finally, in the decline of the response, there seem to be several peaks across the entire spectrum of modulation frequencies. This could maybe be due to a biological phenomenon occurring at a specific and individually different frequency.

7.8.2 Electrode configuration

For the ASSRs in the low frequency ranges the IL configuration seemed to be the best, followed by the IE configuration and with the CL electrode configuration evoking the smallest surfaces. For the high frequency ranges, electrode configurations seemed to have no effect on the dependent variable. From the literature, the following was expected. The generators of the 40 Hz response are believed to be the midbrain and the auditory cortex, whereas the auditory brainstem is thought to activate in response to the 80 Hz ASSR (Purcell et al., 2004) and the higher frequencies are assumed to activate more early stages of the auditory pathway like the AN and the cochlea (Picton, 2013). Keeping this in mind, together with the finding that the electrode placement closest to the neural source measures the highest responses (see 3.3.1.2), we expected that the IE electrode would measure the greatest responses in the high frequency ranges (150-250 Hz, 150-300 Hz and 275-275 Hz) and the IL/CL mastoid electrodes would reveal the greatest responses in the ranges of 75-90 Hz, 80-80 Hz, 40-40 Hz and 35-55 Hz. As auditory information is processed bilaterally as early as the brainstem (see 7.6.3), it is possible

that the IL and CL electrodes measure similar response amplitudes in the latter frequency ranges. However, no significant differences in amplitudes evoked by the noise sweep in all ranges or in response amplitudes to the 40 Hz and 275 Hz AM noise were found between the electrode configurations.

7.9 ASSR and hearing questionnaire analysis

7.9.1 HQ scores

Correlations between all dependent variables of the ASSR (see 5.7.3.2) and HQ score were tested. As stated above, in people with HHL, ABR wave-I amplitude decreases because of damage to the AN (e.g. Kujawa & Liberman, 2009). Because the responses to wave-I and high modulation frequencies presumably are generated by similar structures (Picton, 2013), we expected the response amplitude in the high frequency ranges to decrease with higher scores on the HQ. Because central homeostatic mechanisms are thought to restore reduced activity from the AN (Schaette & McAlpine, 2011), similar responses in the low frequency ranges for the different scores on the HQ in all subjects were expected. Similar to the ABR wave-V/I parameter, an ASSR ratio of amplitudes to the noise sweep in the frequency ranges 150-250 Hz on 35-55 Hz was also tested because this ratio could be more sensitive to detect HHL. Based on figures 23-28, there seems to be a relationship between the responses in the ranges 150-250 Hz, 150-300 Hz, 75-90Hz, 35-55 Hz or the responses to the 40 Hz AM noise and the HQ scores. However, only the responses to the 40 Hz AM noise (IL and IE) were significantly negative correlated with the HQ scores. Thus, the higher the scores on the questionnaire, the smaller the amplitudes elicited from the cortex. This does not correspond to the findings of Schaette & McAlpine (2011) described above. The possible lower sensation level (see 7.5) of the presented stimuli in subjects with higher noise exposure histories, could offer an explanation for this finding.

7.9.2 Groups based on HQ score

All subjects were divided into two groups to gain greater statistical power compared to the correlation analysis in the previous section. Based on figure 29, the responses in all frequency ranges and the responses to the 40 Hz AM noise appeared to be smaller in persons who have been more exposed to noise. However, this is not the case for the responses to the 275 Hz AM noise. This time, the ASSR ratio (150-250 Hz on 35-55 Hz) also seemed smaller in the high noise exposure group. In general, the responses to the noise sweep were significantly smaller in the

high noise exposure group and more specifically the responses in the frequency range 150-250 Hz (IE). This corresponds to our hypothesis since these responses are hypothesized to be generated by the AN, to which HHL causes damage (e.g. Kuwaja & Liberman, 2009). However, as in the previous section, the responses to the 40 Hz AM noise were also significantly lower in the high noise exposure group. This result contradicts the hypothesis that there would be no differences in responses evoked by the cortex in individuals with and without HHL (Schaette & McAlpine, 2011). As described in 7.5, these results should be interpreted with caution.

7.10 ABR vs. ASSR analysis

ABR wave-I amplitude is assumed to be correlated with the ASSRs in high frequency ranges (around 200 Hz). ABR wave-V amplitude, however, is assumed to be correlated with ASSRs in lower frequency ranges (around 80 Hz). For ABR wave-V-I and the wave-V/I ratio, positive correlations with ASSRs in low frequency ranges or negative correlations with ASSRs in high frequency ranges are assumed. Correlations between the ASSR ratio and wave-I are expected to be positive, whereas correlations between the ASSR ratio and wave-V or the ABR ratio are expected to be negative. However, none of these relations was found after applying bivariate correlation analysis. All correlations that were found were opposite to our expectations described above. The significance level of 0.01 causes random significance (type-I errors) in 1% of all comparisons. As many comparisons were carried out (between all the ABR and all the ASSR parameters), the significant correlations we found were probably due to this type-I error. The scatterplots of the correlations between the ABR and ASSR parameters which we expected are included in appendix L.

7.11 Theoretical and practical implications of our research

In this study, no correlates between the ABR and ASSR parameters following our expectations were found. Additionally, the ABR measurements do not provide convincing evidence for HHL in subjects who expose themselves frequently to noise and do not adequately protect themselves. For the ASSR measurements, one parameter is demonstrated to vary with noise exposure as we expected and one parameter against our expectations. However, it is also possible that a difference in sensation level in subjects with varying noise exposure history functions as a mediating variable for this effect. Nevertheless, it is still very important for people to be aware of the risk they expose themselves to because several studies do demonstrate the possible damage that can be induced by HHL (e.g. Kujawa & Liberman, 2009; Shaheen et al.,

2012). Interventions and campaigns should be continued to be organized in order to achieve better sensitization. Also, earplugs should be distributed at festivals, concerts and in discotheques. Additionally, measures should be undertaken to keep a distance from the loudspeakers and to provide lounges were persons can take a break from the loud music exposure (Vogel et al., 2010). Furthermore, the DTT should be widely available on the internet. In this way, adolescents and young adults can test their hearing abilities and are consequently alarmed when a small or moderate HL is present. Maybe, this would lead them to wear hearing protection and take measures against further deterioration. As is already demonstrated in the study Stamper & Johnson (2014), HHL can be detected using ABR. This study possibly demonstrates that HHL can also be detected with ASSR. It is possible that other significant results were not obtained because of the small sample size.

7.12 Limitations

Our study has several limitations. First, the disadvantage of our HQ is that it is not validated nor standardized, in comparison with the study of e.g. Stamper & Johnson (2014), which can cause a discussion about the exactness of the formulation of the questions, the assigment of the scores and the subdivision of the subjects in two groups. In addition, every questionnaire is subject to inadequate recall accuracy and recall bias. Furthermore, every subject has their own interpretation of the questions. Afterwards, a few elements (see 7.3) have been discovered that were not included but did fit in the questionnaire we composed. Another limitation is that we were aware of the study purpose and since the interpretation of the ABR is not fully objective, this could have had an influence on our judgment although we tried to avoid this.

The main limitation of this study, which already appeared several times through this thesis, is the limited sample size (N=13). Because the study of Stamper & Johnson (2014), that was published in the course of the development of our thesis, demonstrated the ABR wave-I to be related to the noise exposure history of subjects with a larger sample size (N=30), we do believe significant outcomes could be found with an expanded sample size. Additionally, since the ABR and the ASSR are in nature similar responses, a relation between the two objective methods is indispensable. We thus expect that a relation can be found in a larger sample size. Finally, because 4 kHz pure tone thresholds seem to differ between the two groups we made, no statements can be done with absolute certainty because all found effects could be due to this difference. However, this difference could also be coincidal and in this case, it is possible that our subjects were not exposed to such an amount of noise that induces HHL and therefore only a few significant decreases in responses were detected.

7.13 Suggestions for follow-up studies

For future studies, the following suggestions are made. First, Furman et al. (2013) compared the proportion of low-SR fibers (<20 spikes/s) between noise exposed and control animals. It was found that this proportion was significantly reduced in the high-frequency region (>4 kHz). In the low-frequency region (≤4 kHz), where noise-exposure effects were minimal, differences were not statistically different. It could therefore be interesting in the future to use stimuli with higher carrier frequencies than 4 kHz, as the HHL above all strikes in the basal part of the cochlea. However, Stamper & Johnson (2014) did demonstrate HHL using the same carrier frequency. However, in their study a relationship between noise exposure background and ABR wave-I amplitude was only found at intensities ≥70 dB nHL, with the relationship decreasing and disappearing at levels ≤60 dB nHL, which is located above the intensity levels used in this study. Therefore, in the future, measurements should be conducted at levels at and above 70 dB nHL.

Additionally, for the ASSR measurements, it would be interesting to assess other parameters in future research. For example, Shaheen et al. (2012) argued that ASSR in response to SAM tones provide a higher SNR than ABR and phase consistency (that can be derived from the ASSR) is less affected by intersubject variability. They demonstrated that the latter parameter (derived from high frequency AM ASSR) would probably be the most robust measurement of HHL in humans. Therefore, it is possible that phase consistency would be a more robust parameter than the ones we used. Furthermore, the parameters that demonstrated significant correlations with the HQ score (biased response amplitude to the 40 Hz AM noise and the mean amplitude to the noise sweep in the range of 150-250 Hz) should be further investigated. Besides, the limitations of this study (see 7.12) should be taken into account in follow-up research. Finally, to be more certain the noise exposure has negatively influenced the auditory periphery, subjects with more evidence of HHL or even hearing-impaired subjects should be included into the test-design. Although, when NH subjects would be tested again, researchers should, prior to the AEP measurements, be reassured there is no significant difference in the pure tone audiograms of subjects.

Conclusion

This study emanated from two main hypotheses. In the first, it is hypothesized that persons that have been exposed more to recreational and occupational noise for the past five years, have lower supra-threshold wave-I ABR amplitudes or smaller ASSR amplitudes at high modulation frequencies, due to HHL. Because variability in ABR and ASSR response amplitude exists, even in NH ears, it is possible that some variability could be due to differences in noise exposure history. In this way, we hoped to contribute to the establishment of a diagnostic test to detect HL before thresholds are affected. To test the first hypothesis, the subjects filled in a self made HQ, which mainly queries for recreational noise exposure. Two groups were subsequently created, based on the scores of the HQ: lower (group 1) and higher (group 2) noise exposed subjects. In summary the following results concerning this hypothesis were obtained. Between the ABR parameters and the HQ scores existed no significant correlations, nor between groups based on the HQ scores were significant differences. Furthermore, there was found a significant correlation between the responses to the 40 Hz AM noise and the HQ scores (IL and IE). Between the two groups based on the HQ scores, smaller responses to the noise sweep were found for the high noise exposure group in general and more specifically in the range 150-250 Hz (IE). Also, the responses to the 40 Hz AM noise ASSR were greater for the low noise exposure group, in comparison with the high noise exposure group. The variation of the responses to the low frequencies with noise exposure score contradicts the hypothesis, whereas the variation of the responses in the high frequency ranges supports the hypothesis. Due to possible differences in the sensation level of the applied stimuli between groups, these results should be interpreted with caution.

In the second hypothesis, it is hypothesized that high-frequency ASSR and ABR wave-I measurements are related because both responses share the same generator (the AN). Assessment of wave-I at supra-threshold levels could help in diagnosing HHL in humans if the response amplitudes are smaller than expected, because this indicates less AN input. An ASSR correlate could thus provide a more robust representation of wave-I and consequently a more robust diagnostic test for HHL. Unfortunately, this wave is hard to detect in many conditions and especially at low- and mid-intensity levels. To assess the second hypothesis, both objective methods were incorporated in our experimental design. However, for the ABR vs. ASSR analysis no correlations that met our expectations were found. More subjects should be tested in further research to obtain significant correlations, since these responses are in nature similar. Furthermore, AEPs in many different conditions were analysed, since a gap exists in literature

in information on the protocols of this kind of experimental design. As to the stimuli, one should always search for a balance between accuracy in the frequency domain and accuracy in the time domain. The electrode configuration that measured the clearest amplitudes was the one closest to the neural generator of the response.

Since this research only provided a preview on the possibilities of objective audiometry for diagnosing HHL, further research with a larger sample size and at higher intensities is needed to obtain more information about which test protocol is best used to detect this kind of HL. If objective diagnosis of HHL could be possible, this would be an important step forward into the sensitization of the society into better protection and other interventions against hearing damage in adolescents and young adults.

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Appendices

Appendix A. *The underlying physiology of the mechanisms giving rise to HHL.*

It clearly has been demonstrated in animals that dramatic noise exposure causes immediate loss of synapses between IHC and afferent nerve terminals and long-term neurodegeneration. The underlying physiology of HHL will be explained in this section by giving a review of the findings of different studies. The loss of synapses can be explained in the following way: acoustic overexposure causes dramatic swelling of AN terminals in the IHC area (Liberman & Mulroy, 1982; Robertson, 1983). Therefore, it is thought that noise exposure causes damage to the afferent nerve terminals via glutamate-excitotoxicity of the AMPA receptors in the afferent synapses. Kujawa & Liberman (2009) presented three arguments to support this hypothesis: (1) the phenomenon can be imitated by glutamate receptor agonists (Pujol et al., 1993), (2) it can be counteracted by glutamate receptor antagonists (Ruel et al., 2000) and (3) it is not present in the nerve terminals of type II AN which contact the OHC (Robertson, 1983) and express no AMPA receptors (Matsubara et al., 1996; Liberman et al., 2011). The post exposure retraction of nerve terminals is thought to be followed by slow neurodegeneration because of blockade of the neurothrophin cascade. The most important neurotrophin, NT-3, is normally released by the IHC in response to neuregulin, that is released by the AN. Stankovic et al. (2004) demonstrated that blockading this cascade leads to primary neural degeneration. In HHL, the increased distance between peripheral nerve terminals and the IHC due to noise overexposure may suppress the same cascade (Kujawa & Liberman, 2009).

AN fibers in human can be subdivided into two populations: fibers with high-SR (>20 spikes/s) and low thresholds of activation (60%) and fibers with low-SR (<20 spikes/s) and high thresholds of activation (40%). Multiple innervation of the IHC is thus important, since the AN fibers differ in spontaneous discharge rate and threshold to acoustic stimulation (Liberman, 1978). The clear difference in central projections of the low-SR and high-SR AN fibers, have created the idea that these two parts of the bimodal distribution play different roles in auditory processing. Furman et al. (2013) suggested that low-SR fibers could be more vulnerable to this glutamate excitotoxicity. They provided the following explanations: (1) The GLAST transporter, which clears glutamate from the synaptic cleft is less present on the low-SR side (modiolar) of the IHC (Furness & Lawton, 2003). (2) Low-SR fibers contain much less mitochondria than high-SR fibers and mitochondria are an important source of Ca^{2+} buffering (Szydlowska & Tymianski, 2010). Ca^{2+} entry is a protective factor in the glutamate-excitotoxicity and therefore, low-SR fibers are less well equipped to deal with constant glutamate release.

Appendix B. *Number of subjects in the different conditions.*

Condition	Number of subjects
Tone sweep 70-600 Hz	11
Noise sweep 70-600 Hz	10
AM tone 30 Hz	13
Noise sweep 35-300 Hz	13
CE-chirp 50 dB nHL	13
CE-chirp 60 dB nHL	13
Click 50 dB nHL	13
Click 60 dB nHL	13
Toneburst 50 dB nHL	13
4 kHz chirp 50 dB nHL	13
AM noise 275 Hz	6
AM noise 40 Hz	6

Appendix C. *Description of the elements of our hearing questionnaire extracted from other studies.*

Feder et al. (2013) demonstrated that subjects using a portable audio player for more than five years and subjects who reported listening for more than six hours per week to it tuned the volume of their portable audio player at a higher level and had higher high-frequency hearing thresholds. They also measured the sound pressure level of the portable audio player at typical volume settings and found a positive relationship with hearing thresholds. Keeping this results in mind, the following elements from their HQ were adopted: 'for how many years have you been using a portable audio player?', 'how much time do you spend listening to it (frequency)?', 'at what volume settings do you usually listen (intensity)?' and 'at which locations do you listen to your portable audio player?'. Furthermore, a considerable amount of subjects reported symptoms designating TTS that could be attributed to their portable audio player listening behaviour. As we have seen before, TTS could have long-term effects for our hearing ability in the form of HHL. Also tinnitus, a possible consequence of HHL, was often reported being experienced. Additionally, subjects who thought the doctor could restore their hearing ability when impaired due to loud noise exposure, had lower average hearing acuity. Therefore, also the self-reported hearing questions about HL symptoms and hearing health were translated to Dutch and adopted. Finally, the study of Feder et al. (2013) also considered other leisure noise exposure that could influence the TTS. Therefore, we also ask for hobbies and other activities in noisy environments in our HQ. This is an indirect question about occupational noise exposure, in addition to recreational noise exposure.

In addition, Vogel et al. (2010) stated risk behaviour to include frequent and long presence in discotheques and standing close to loudspeakers. Protective behaviours included the use of earplugs and taking breaks during their presence at discotheques. These elements were included in the second section of our HQ, that attempts to measure the amount of noise exposure subjects have been exposed to for the past five years. Demonstrating these risk behaviours and not participating in these protective behaviours was considered to be a potential indicator of HHL. From the HQ used in the study of Tung & Chao (2013), the self-evaluating question about the amount of noise in the hearing environment and all self-reported hearing questions were incorporated in the third section of our HQ, and locations of using earphones in the second. The remaining questions were either created by ourselves based on our experience as young adults in noisy environments or constructed combining ideas from these three studies, e.g. in the first part of our HQ ('history of ear problems') questions were combined from the three studies' background data/demographic variables.

Appendix D. *The self made hearing questionnaire.* Scores connected to the different answer possibilities are designated in yellow.

Algemeen (vul in)

Code (in te vullen door proefleider):……..

Geslacht: man – vrouw

Geschiedenis van oorproblemen (duid het bolletje aan dat van toepassing is)

1. Heeft/ Had u een oorproblematiek? (frequente middenooronsteking, trommelvliesperforatie, oortrauma, zwemmersoor, otosclerose (= verkalking van de beentjesketen),…)
   - Vroeger (wanneer?):……..0,5
   - Nu 1
   - Neen 0

   Welke? (in te vullen wanneer u 'vroeger' of 'nu' antwoordde)

   ……
2. Bekend gehoorverlies aan de linkerzijde?
   - Vroeger (wanneer?):…….. 0,5
   - Nu 1
   - Neen 0

   Oorzaak (in te vullen wanneer u 'vroeger' of 'nu' antwoordde):

   ……..
3. Bekend gehoorverlies aan de rechterzijde?
   - Vroeger (wanneer?):…….. 0,5
   - Nu 1
   - Neen 0

   Oorzaak (in te vullen wanneer u 'vroeger' of 'nu' antwoordde):

   ……..
4. Heeft/Had u last van tinnitus (= oorsuizen, een zoemend, ruizend of helder klinkend geluid in je oren zonder dat een externe stimulus hier aanleiding toe geeft)?
   - JA 1
   - NEE 0

   Zo ja, oorzaak?:……..
5. Heeft/Had u trommelvliesbuisjes?
   - JA 0,5
   - NEE 0

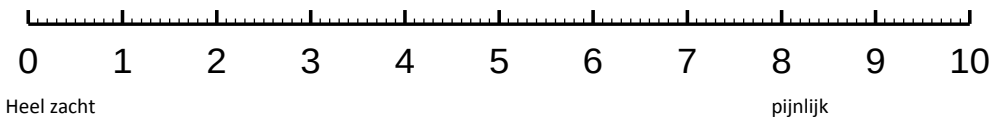
   Zo ja, wanneer?:……..
6. Zijn er gehoorproblemen gekend in de familie (doofheid/slechthorendheid)?
   - JA 0,5
   - NEE 0

   Zo ja, welke?:……

Per activiteit (beantwoord de vragen met de afgelopen 5 jaar in gedachten)

Festival (duid het bolletje aan dat van toepassing is)

7. Frequentie (per jaar): 0x = 0; 1-2x = 0,5; >2x = 1
8. Duur (dagen of uren per keer): ≤ 1 = 0; 2 = 0,5; >2 = 1
9. Intensiteit van de muziek (duid aan met een kruisje op volgende schaal)



<6 = 0; ≥ 6 = 0,5; ≥8 = 1

10. Beschermingsmaatregelen

Oordopjes: o nooit 2 o soms 1 o vaak 0,5 o altijd 0

Pauzes (van de blootstelling aan muziek): o nooit 2 o soms 1 o vaak 0,5 o altijd 0

11. Tijdelijke symptomen achteraf

Last van tinnitus (= oorsuizen): o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Pijn aan de oren: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Moeilijkheden met horen: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

12. Risicogedrag

Dichter dan 2 meter bij de boxen: o nooit 0 o soms 0,5 o vaak 1 o op elk festival 2

Fuif/discotheek (duid het bolletje aan dat van toepassing is)

13. Frequentie (aantal keer per maand): 1-2x = 0; >2 = 1; >4 = 2

14. Duur per fuif: 3-4 = 0; 5 = 0,5; >5 = 1

15. Intensiteit van de muziek (duid aan met een kruisje op volgende schaal)

<6 = 0; ≥ 6 = 0,5; ≥8 = 1

16. Beschermingsmaatregelen

Oordopjes: o nooit 2 o soms 1 o vaak 0,5 o altijd 0

Pauzes (van de blootstelling aan muziek): o nooit 2 o soms 1 o vaak 0,5 o altijd 0

17. Symptomen achteraf

Last van tinnitus (= oorsuizen): o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Pijn aan de oren: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Moeilijkheden met horen: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

18. Risicogedrag

Dichter dan 2 meter bij de boxen: o nooit 0 o soms 0,5 o vaak 1 o op elk festival 2

Concert (duid het bolletje aan dat van toepassing is)

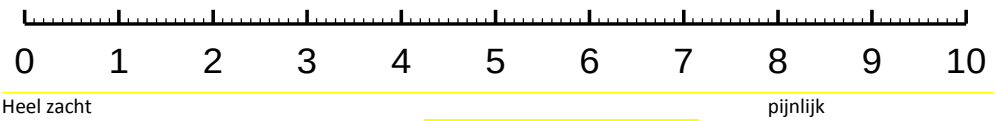
19. Wat voor concert? Welke muziekstijl?

- Moderne muziek (pop/rock/metal/…) 0,5
- Klassieke muziek 0,5

20. Frequentie (per jaar): 1-2x = 0; 3x = 0,5: >3x = 1

21. Duur van het concert: 2-3 = 0; >3 = 1

22. Intensiteit van de muziek (duidt aan met een kruisje op volgende schaal)



<6 = 0; ≥ 6 = 0,5; ≥8 = 1

23. Beschermingsmaatregelen

Oordopjes: o nooit 2 o soms 1 o vaak 0,5 o altijd 0

Pauzes (van de blootstelling aan muziek): o nooit 2 o soms 1 o vaak 0,5 o altijd 0

24. Symptomen achteraf

Last van tinnitus (= oorsuizen): o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Pijn aan de oren: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

Moeilijkheden met horen: o nooit 0 o soms 0,5 o vaak 1 o na elk festival 0

25. Risicogedrag

Dichter dan 2 meter bij de boxen: o nooit 0 o soms 0,5 o vaak 1 o op elk festival 2

MP3/iPod gebruik (duid het bolletje aan dat van toepassing is)

26. Gebruikt u een MP3/iPod? o JA 0,5 o NEE 0

Indien 'nee', ga dan naar vraag 31

Indien 'ja', hoeveel jaar gebruikt u reeds een iPod/MP3?

1-2 = 0; 3-4 = 0,5; ≥5 = 1

27. Frequentie
    - Zelden, niet meer dan 1x per maand 0
    - Niet vaak, 1-3x per maand 0
    - Soms, 1-2x per week 0,5
    - Vaak, 3-5x per week 1
    - Heel vaak, iedere dag 1,5
    - Bijna altijd, meermaals per dag 2

28. Duur (vul in): Aantal uur per dag waarin geluisterd werd:

≤ 0,5 = 0; 0,5-1 = 0,5; >1 = 1; >3 = 2

29. Volume/Intensiteit (duid aan met een kruisje op volgende schaal)

<6 = 0; ≥ 6 = 0,5; ≥8 = 1

30. Locaties van gebruik (er mogen meerdere bolletjes aangeduid worden)

1 = 0; 2 = 0,5; 3-4 = 1; 5-6 = 1,5; 7-8-9 = 2

- Thuis
- Op school
- Bibliotheek
- In de auto
- Openbaar vervoer
- Op openbare plaatsen
- In bed
- Op de fiets
- Andere: ……

Hobby's met veel muziek/lawaai

31. Welke hobby's doet u die gerelateerd kunnen zijn aan een lawaaierige omgeving? 1= 1; geen = 0, meerdere = 2

- DJ
- Muziek spelen (=een instrument bespelen)
- Bandje/harmonie/fanfare/…
- Balsport (voetbal, basketbal,…)
- Andere:……
- Geen

Andere activiteiten in lawaaierige omgeving

32. Doet u andere activiteiten in een lawaaierige omgeving? (bv. sportactiviteiten, cafébezoek met veel lawaai, live sportwedstrijd bijwonen, werk in lawaaierige omgeving, paintball, jagen, werken als leerkracht (in de klas/op de speelplaats/…), muziek spelen, cinema, in de sporthal, …)

- JA 1 als ≤ 1x/week en 2 als > 1x/week
- NEE 0

Zo ja?

- Welke?.....
- Hoe vaak per week?.....
- Hoe lang (= aantal uur per dag dat zo'n activiteit wordt uitgevoerd)? > 2 = 1; ≤2 = 0
- Draagt u gehoorbescherming in deze situatie(s)? (bv. op werkplaats, sporthal, …): o JA 0 o NEE 1

Zelfevaluatie (duid het bolletje aan dat van toepassing is)

33. Hoe lawaaierig vind je je eigen levensstijl?
    - Heel erg lawaaierig 2
    - Lawaaierig 1
    - Normaal 0
    - Niet lawaaierig 0
    - Heel erg stil 0
34. Ik krijg klachten over het feit dat ik de tv en/of de radio te luid zet
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
35. Ik kan de telefoon niet horen afgaan in een andere kamer
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
36. Ik moet vragen om herhaling omdat ik de ander niet versta
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
37. Ik moet me hard concentreren om mensen te verstaan, zelfs zonder rumoer
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
38. Ik kan in lawaaierige omgevingen niet met anderen praten
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
39. In vergaderingen of discussies versta ik mensen verkeerd
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
40. Ik heb meer moeite dan anderen in het algemeen om mensen te verstaan in lawaaierige omgevingen
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
41. Ik moet vooraan in de klas/een ruimte zitten om de spreker goed te verstaan
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
42. Ik hoor de deurbel en/of de telefoon niet
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
43. Ik heb last van tinnitus/oorsuizen (een zoemend, ruizend of helder klinkend geluid in je oren zonder reden)
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
44. Ik zet het volume van mijn MP3/ iPod tijdens het luisteren luider omdat ik na een tijdje gewoon word aan de luidheid
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
45. Ik denk dat ik risico loop/ gelopen heb op gehoorverlies
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
46. Ik denk dat de arts mijn gehoor weer normaal kan maken als mijn gehoor niet weer vanzelf normaal wordt na blootstelling aan hard lawaai of harde muziek
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2
47. Anderen klagen soms dat ze de muziek horen die ik afspeel op mijn MP3/iPod
    o nooit 0 o soms 0,5 o vaak 1 o altijd 2

Appendix E. *The individual results of the PTA and APEX threshold measurements.*

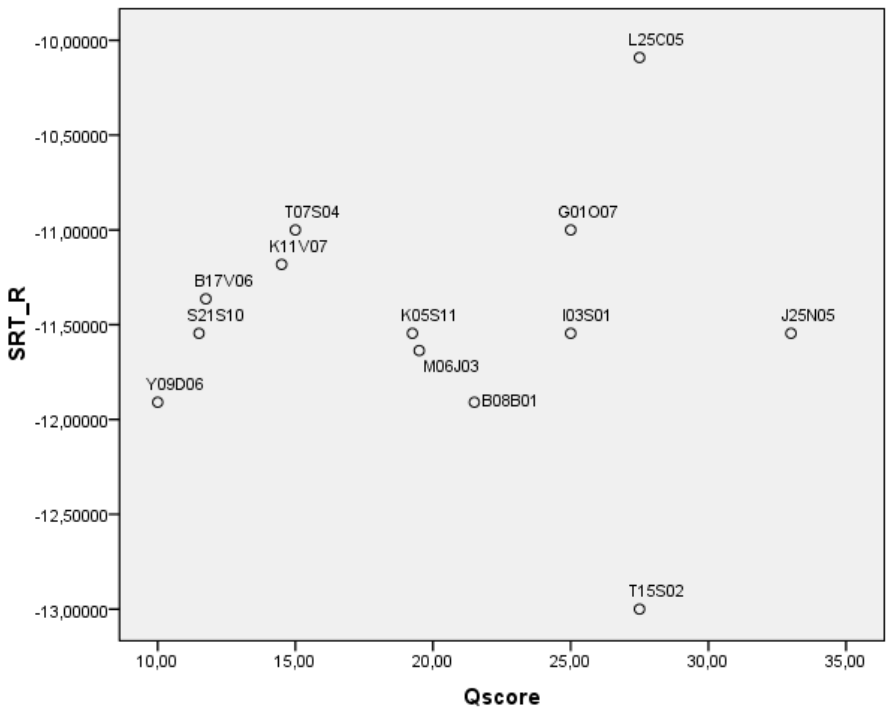
		Subjects												
Measurement	Stimulus	B08B01	B17B06	G01O07	I03S01	J25N06	K05S11	K11V07	L25C05	M06J03	S21S10	T07S04	T15S02	Y09D06
PTA (in dB HL)	125	5	-5	15	10	15	10	10	10	10	20	10	5	5
	250	10	-5	10	5	10	0	0	5	10	10	15	10	0
	500	5	0	15	10	0	0	0	10	5	15	15	5	0
	1000	10	5	10	20	5	10	5	15	0	0	15	15	0
	2000	10	-5	5	-5	0	20	0	10	-5	-5	0	5	10
	4000	15	5	10	5	5	-5	0	10	-5	5	-10	10	10
	8000	-10	5	15	10	15	0	0	15	-5	5	5	10	20
APEX (in dB p-peSPL)	Click	35	35	35	30	35	40	35	40	30	35	35	40	40
	Toneburst	30	25	25	20	25	25	25	30	20	20	25	35	30
	NB Chirp	25	25	30	20	25	25	25	35	25	25	25	35	30
	CE Chirp	30	40	35	30	35	35	30	35	40	30	30	40	40

Appendix F. *The results of the SRT measurement.*

(a) SRT (in dB SNR), HQ scores, pure tone averages over the frequencies 1, 2, 4 and 8 kHz (in dB HL) and hearing thresholds for the different short-duration stimuli of the ABR measurements (in dB p-peSPL) per subject.

Subject ID	SRT	HQ score	PTA 1,2,4,8	HT click	HT CE-chirp	HT NB CE-chirp	HT TB
Y09D06	-11.90909	10.00	10	40	40	30	30
S21S10	-11.54545	11.50	1.25	35	30	25	20
B17V06	-11.36364	11.75	2.5	35	40	25	25
K11V07	-11.18182	14.50	1.25	35	30	25	25
T07S04	-11.00000	15.00	2.5	35	30	25	25
K05S11	-11.54545	19.25	6.25	40	35	25	25
M06J03	-11.63640	19.50	0	30	40	25	20
B08B01	-11.90909	21.50	6.25	35	30	25	30
I03S01	-11.54545	25.00	7.5	30	30	20	20
G01O07	-11.00000	25.00	10	35	35	30	25
T15S02	-13.00000	27.50	10	40	40	35	35
L25C05	-10.09090	27.50	12.5	40	35	35	30
J25N05	-11.54545	33.00	6.25	35	35	25	25

(b) Scatterplot of the Speech Reception Threshold (SRT) of the right ear vs. questionnaire score of all subjects.

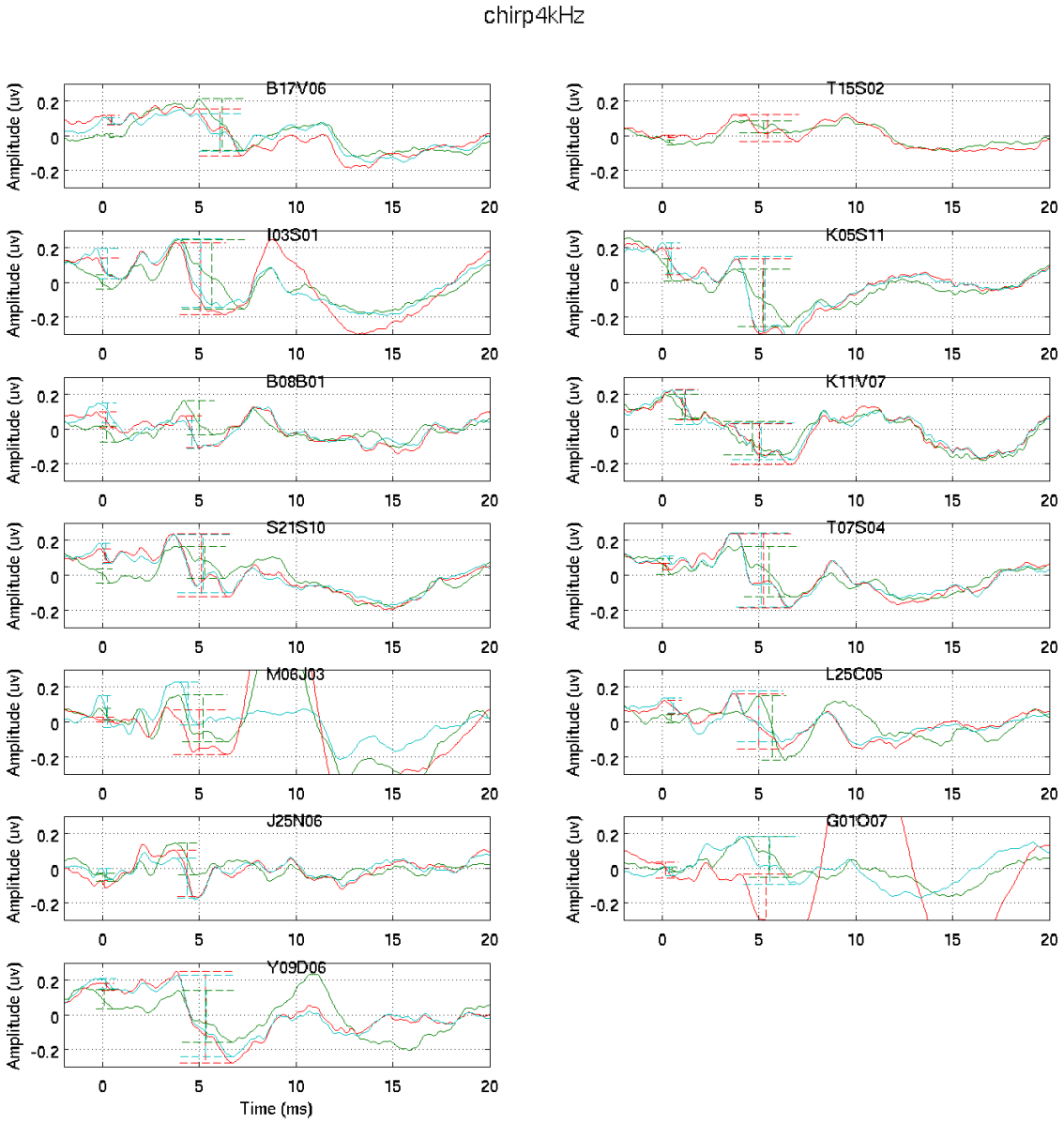


Appendix G. *The results of the ABR measurements.*

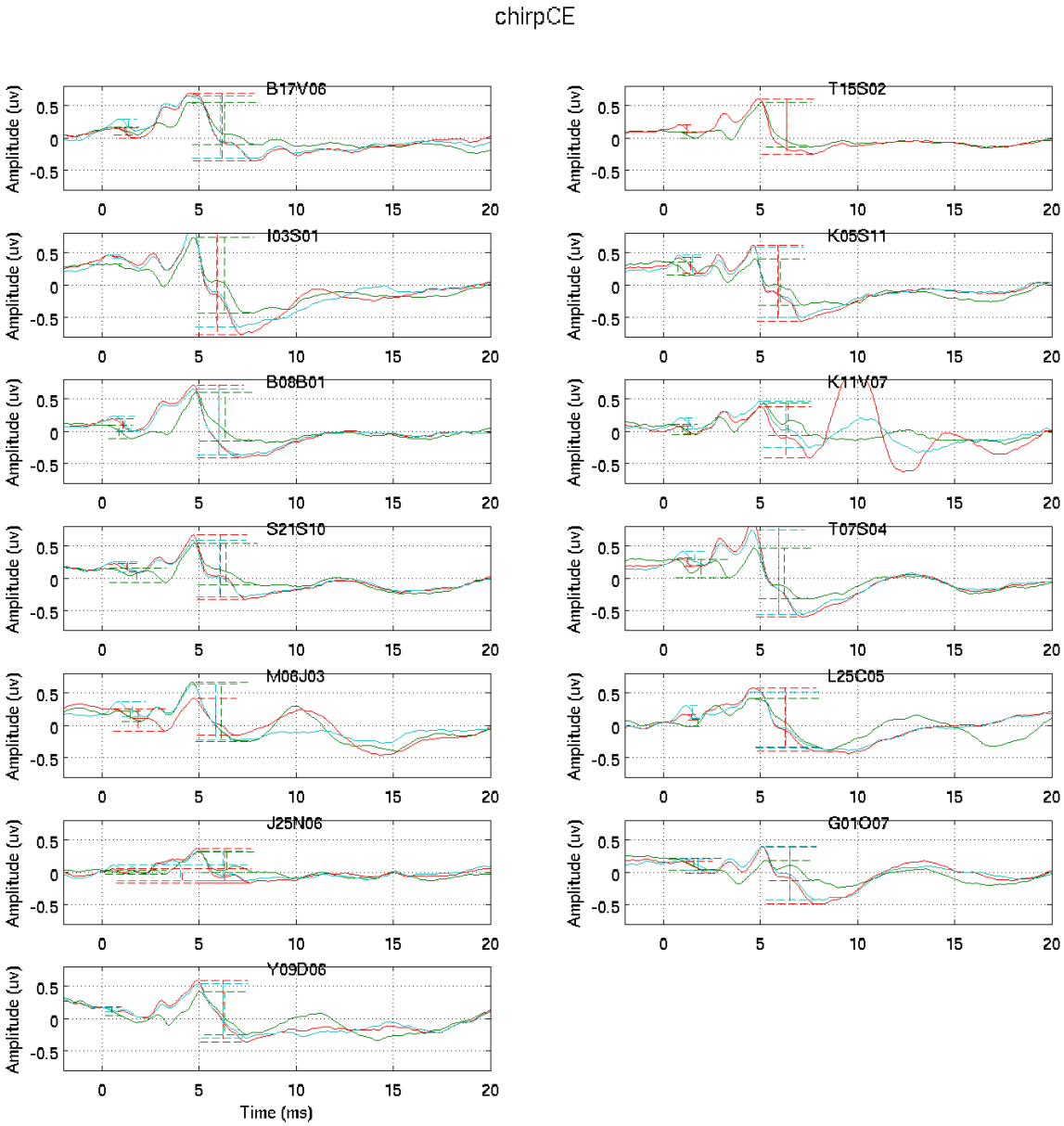
(a) Ranges, minima, maxima, means, standard deviations (SD) of the ABR peak-to-peak amplitudes of wave I and wave V, per stimulus and electrode configuration (in µV).

W	EC	Stimulus	Range	Minimum	Maximum	Mean	SD
I	IE	4kHz chirp	0.143	0.040	0.183	0.102	0.052
		CE-chirp	0.144	0.051	0.195	0.125	0.049
		Click	0.216	0.063	0.279	0.135	0.060
		Toneburst	0.177	0.044	0.221	0.105	0.052
I	IL	4kHz chirp	0.137	0.016	0.153	0.071	0.039
		CE-chirp	0.148	0.025	0.173	0.107	0.041
		Click	0.185	0.052	0.237	0.100	0.059
		Toneburst	0.115	0.039	0.154	0.088	0.035
V	CL	4kHz chirp	0.331	0.067	0.398	0.255	0.090
		CE-chirp	0.854	0.309	1.163	0.679	0.225
		Click	0.580	0.185	0.765	0.447	0.168
		Toneburst	0.286	0.093	0.379	0.243	0.085
V	IE	4kHz chirp	0.312	0.158	0.470	0.311	0.107
		CE-chirp	1.076	0.458	1.534	0.944	0.275
		Click	0.470	0.427	0.897	0.571	0.160
		Toneburst	0.313	0.127	0.440	0.304	0.098
V	IL	4kHz chirp	0.374	0.157	0.531	0.329	0.114
		CE-chirp	1.120	0.531	1.651	1.000	0.317
		Click	0.664	0.328	0.992	0.598	0.196
		Toneburst	0.309	0.196	0.505	0.332	0.110

(b) The individual waveforms of the ABR measurements, per stimulus. The red line represents the IL electrode configuration, the blue line represents the IE electrode configuration and the green line represents the CL electrode configuration. The digital determination of the peaks and throughs of wave-V and wave-I is indicated by the dashed lines. The adjustments we have made to the digitally derived peak-to-peak amplitude of wave-I (see 5.7.3.1) are shown in a table below each image. The CL wave-I amplitude was not included in the analyses.

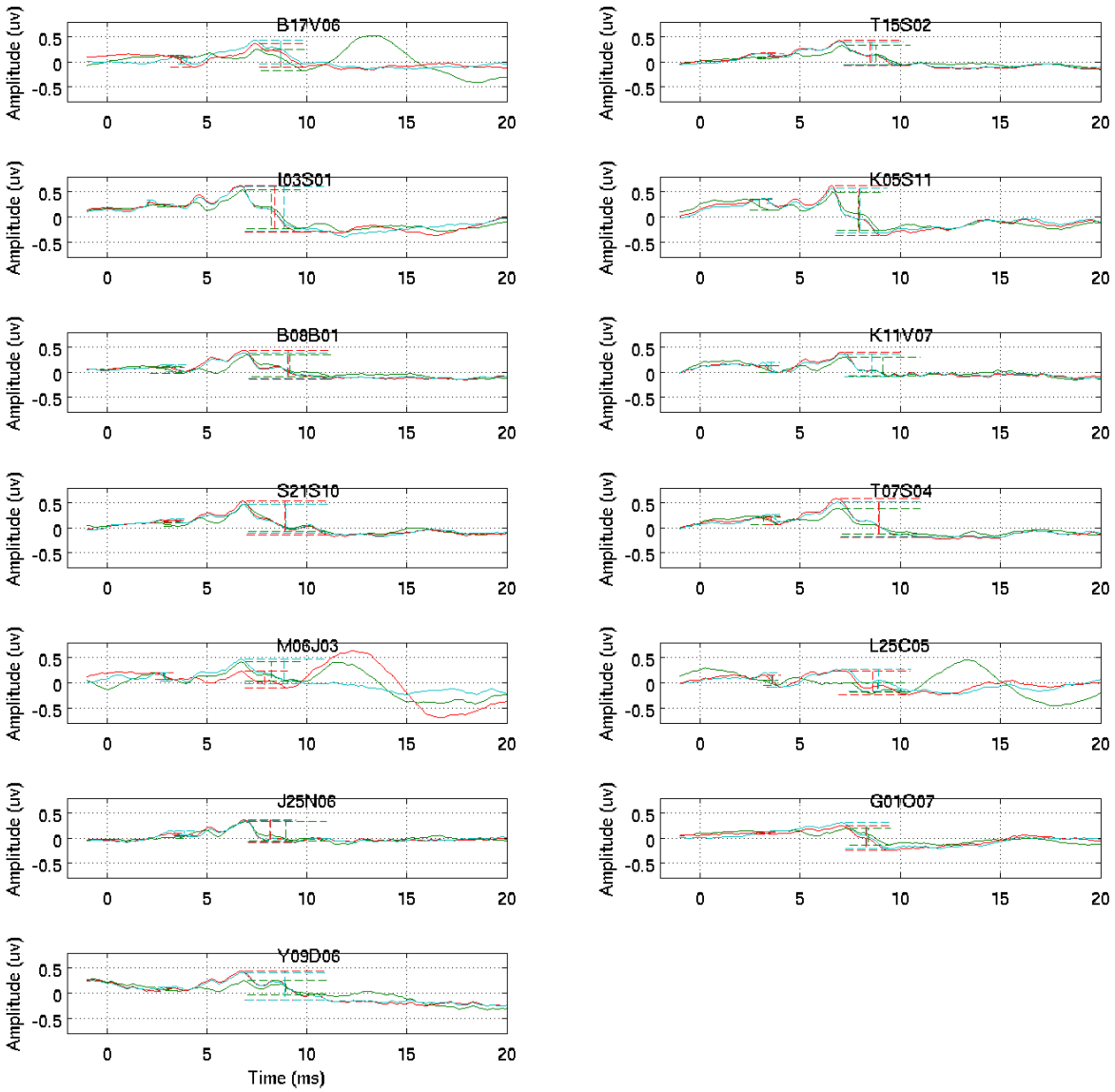


Adjustments			
Subject ID	Wave	Electrodeconfiguration	Operation
K11V07	I	IL	:2
K11V07	I	IE	:2

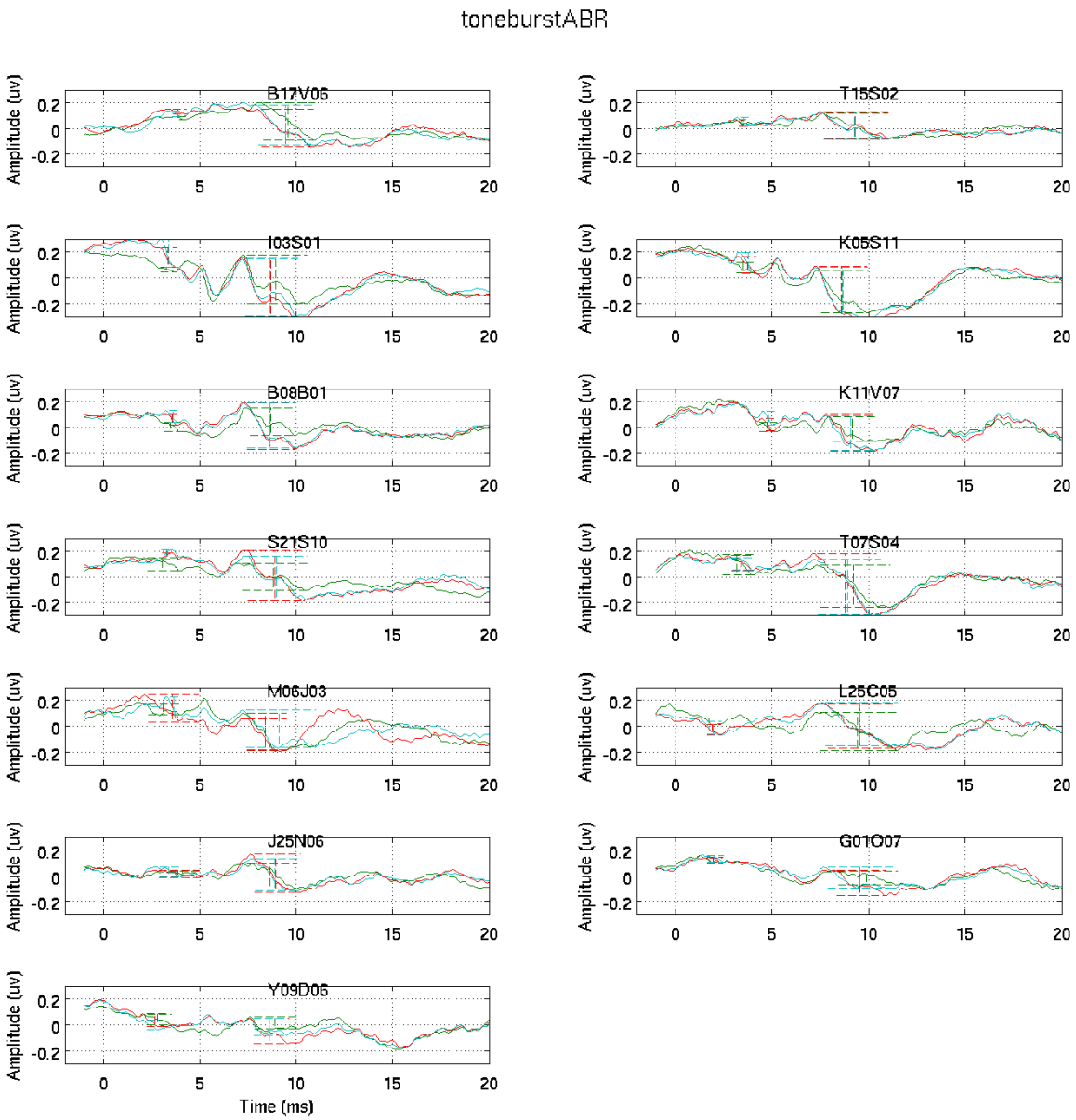


Adjustments			
Subject ID	Wave	Electrodeconfiguration	Operation
B08B01	I	IL	:1.5
B08B01	I	IE	:1.5
S21S10	I	IL	:1.5
S21S10	I	IE	:1.5
M06J03	I	IL	:2
M06J03	I	IE	:2
J25N06	I	IL	:3
J25N06	I	IE	:3
K05S11	I	IL	:2
K05S11	I	IE	:2
T07S04	I	IE	:1.5
G01O07	I	IL	:2
G01O07	I	IE	:2

clickABR



Adjustments			
Subject ID	Wave	Electrodeconfiguration	Operation
Y09D06	I	IL	x1.5
Y09D06	I	IE	x1.5

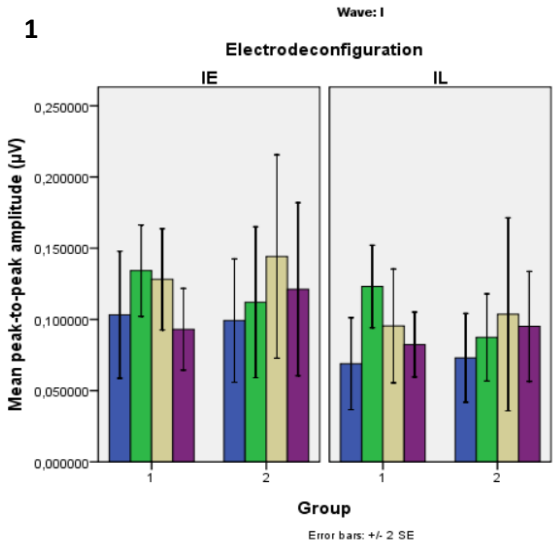


Adjustments			
Subject ID	Wave	Electrodeconfiguration	Operation
M06J03	I	IL	:2
K05S11	I	IL	:2
K05S11	I	IE	:2
L25C05	I	IL	x1.5
L25C05	I	IE	x1.5

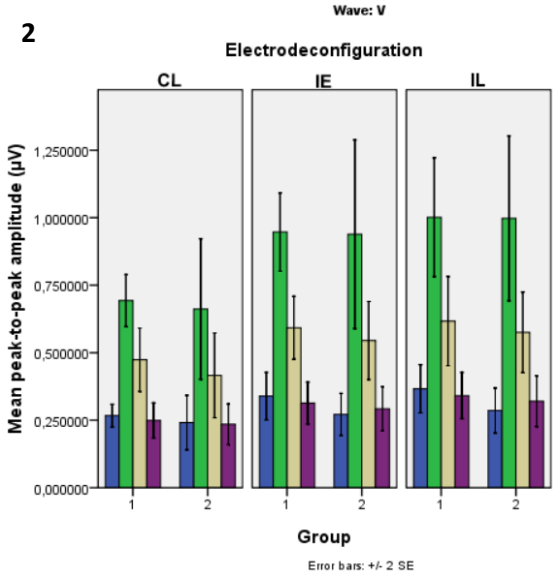
Appendix H. *Mean amplitudes of wave-I (1), wave-V (2), wave-V-I (3) and the mean ABR ratio wave-V/I (4) for the different stimuli, electrode configurations and groups.*

Group 1 = lower noise exposure, group 2 = higher noise exposure, blue = the 4 kHz chirp, green = the CE-chirp, yellow = the click, purple = the toneburst.

1



2



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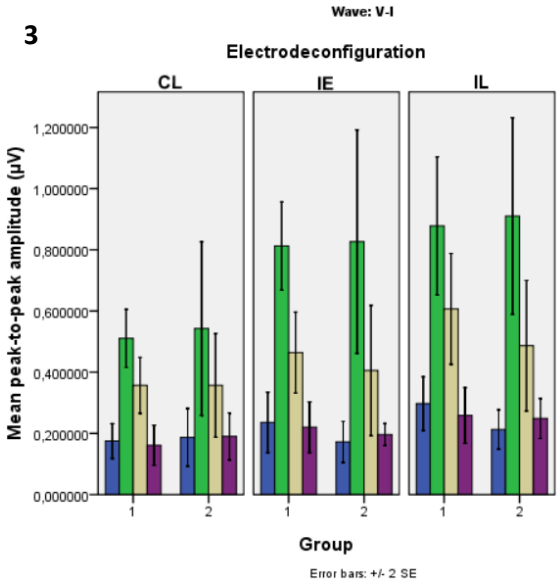
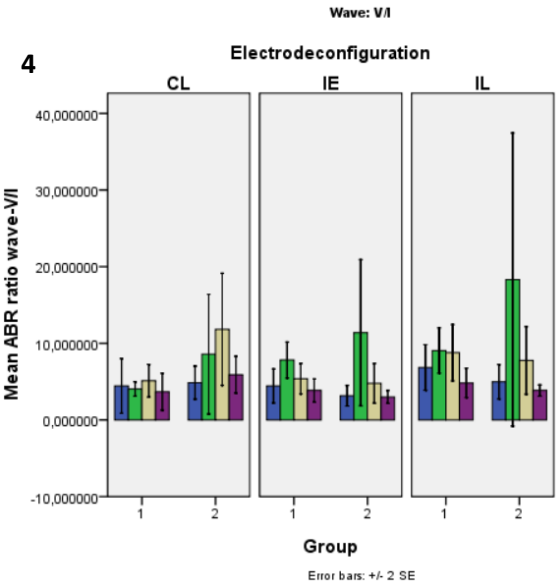


4

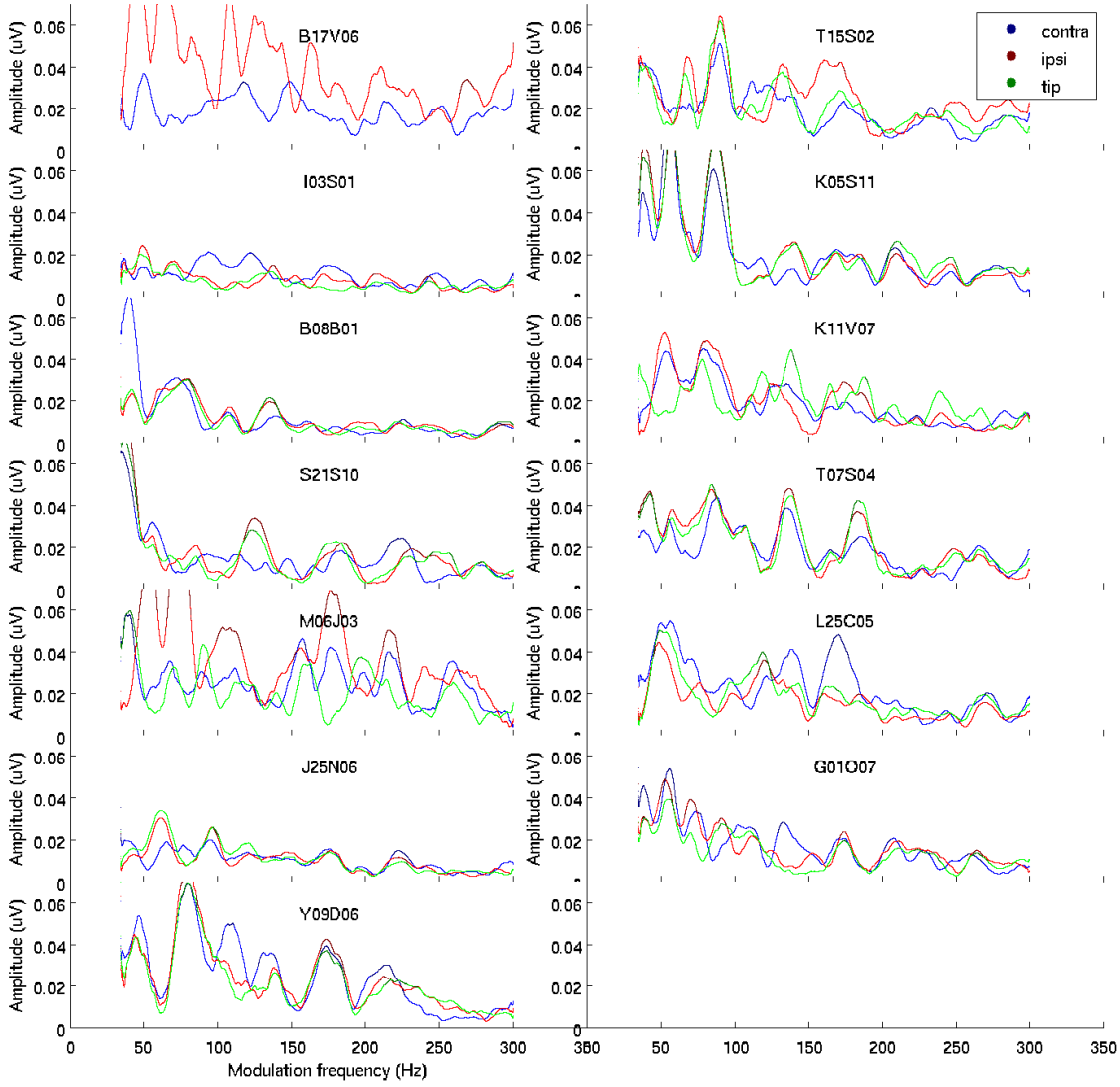


Appendix I. *The results of the ASSR measurements.*

(a) Ranges, minima, maxima, means, standard deviations (SD) of mean ASSR response amplitudes to the noise sweep in different frequency ranges per electrode configuration (in μV).

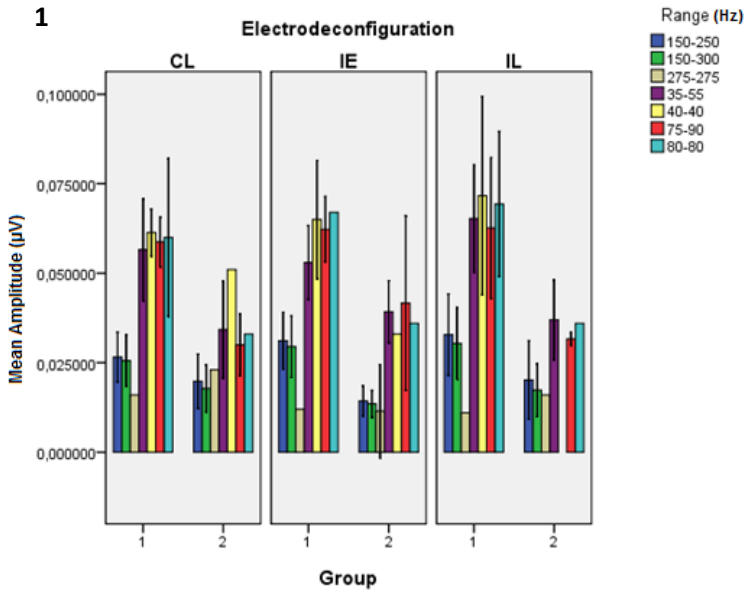
Range	EC	Range	Minimum	Maximum	Mean	SD
150-250	CL	0.034	0.011	0.045	0.023	0.010
	IE	0.033	0.008	0.041	0.023	0.012
	IL	0.045	0.010	0.055	0.027	0.015
150-300	CL	0.035	0.010	0.045	0.022	0.009
	IE	0.031	0.008	0.039	0.022	0.011
	IL	0.046	0.009	0.055	0.024	0.013
275-275	CL	0.007	0.016	0.023	0.020	0.005
	IE	0.013	0.005	0.018	0.012	0.007
	IL	0.005	0.011	0.016	0.014	0.004
35-55	CL	0.050	0.021	0.071	0.047	0.018
	IE	0.036	0.029	0.065	0.047	0.012
	IL	0.056	0.023	0.079	0.051	0.019
40-40	CL	0.015	0.051	0.066	0.059	0.007
	IE	0.045	0.033	0.078	0.059	0.020
	IL	0.043	0.044	0.087	0.072	0.024
75-90	CL	0.045	0.023	0.068	0.046	0.017
	IE	0.043	0.029	0.072	0.053	0.018
	IL	0.069	0.027	0.096	0.052	0.025
80-80	CL	0.038	0.033	0.071	0.051	0.019
	IE	0.031	0.036	0.067	0.052	0.022
	IL	0.050	0.036	0.086	0.061	0.022

(b) *The individual responses to the noise sweep per electrode configuration of the ASSR measurements.* The red line represents the IL electrode configuration, the blue line represents the CL electrode configuration and the green line represents the IE electrode configuration. Dark colors indicate significant responses.

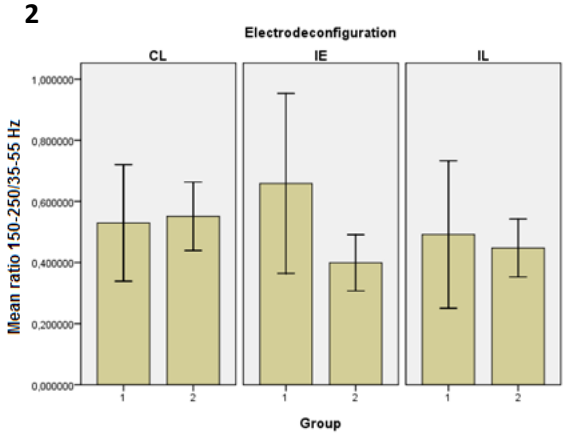


Appendix J. *Mean ASSR amplitudes to the noise sweep in different frequency ranges (1) and the mean ASSR ratio (150-250 Hz/35-55 Hz) (2) and mean ASSR amplitudes to the 40 Hz and 275 Hz AM noise (3) for the different electrodeconfigurations and groups (group 1 = lower noise exposure and group 2 = higher noise exposure).* Error bars of + and - 2 standard errors are shown.

1



2



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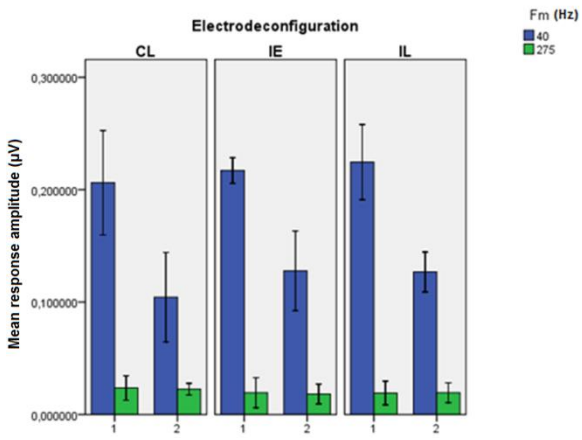
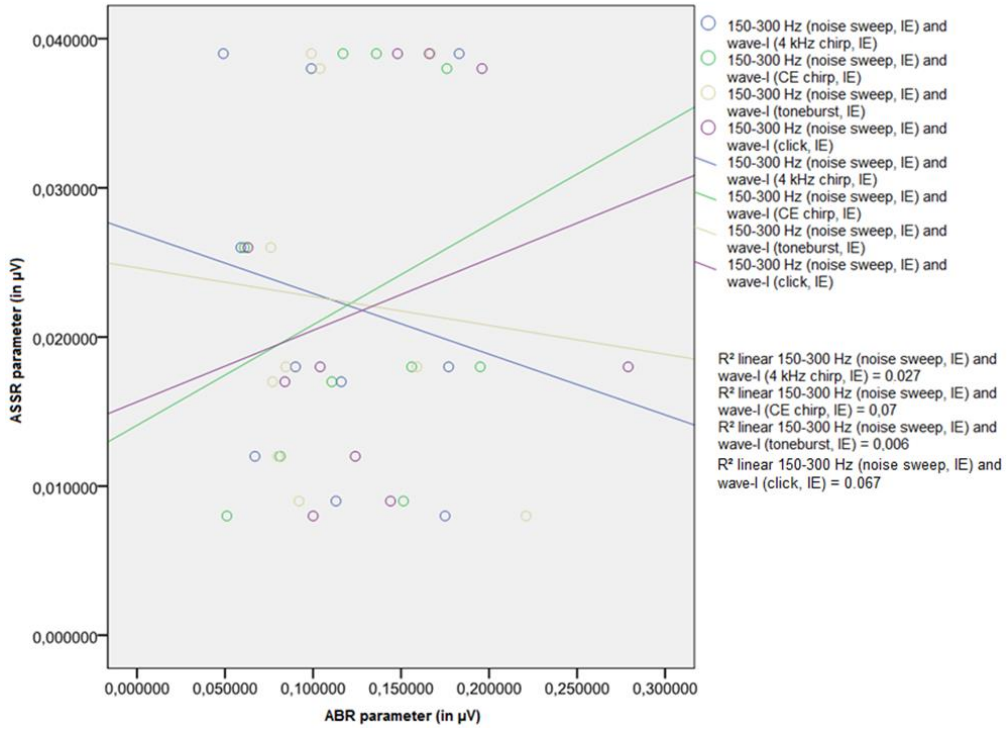


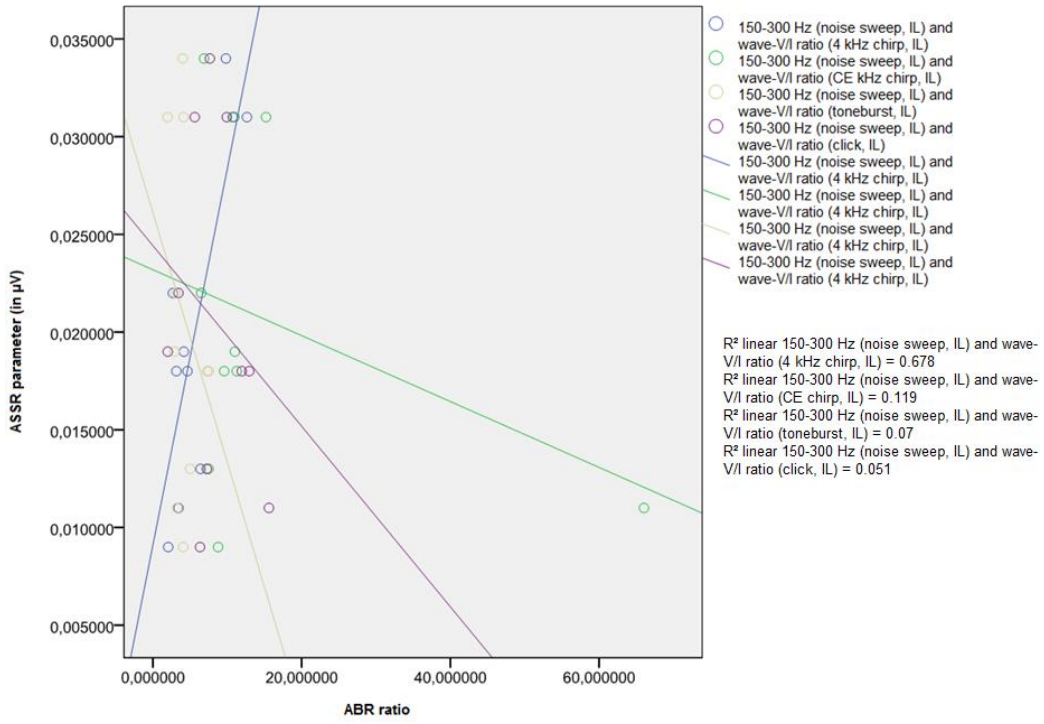
Appendix K. *Comparison of ABR amplitudes to the toneburst, the click, the CE-chirp and the narrowband CE-chirp with ABR amplitudes in literature*. Stim. = stimulus, TB= toneburst, p-t-p = peak-to-peak.

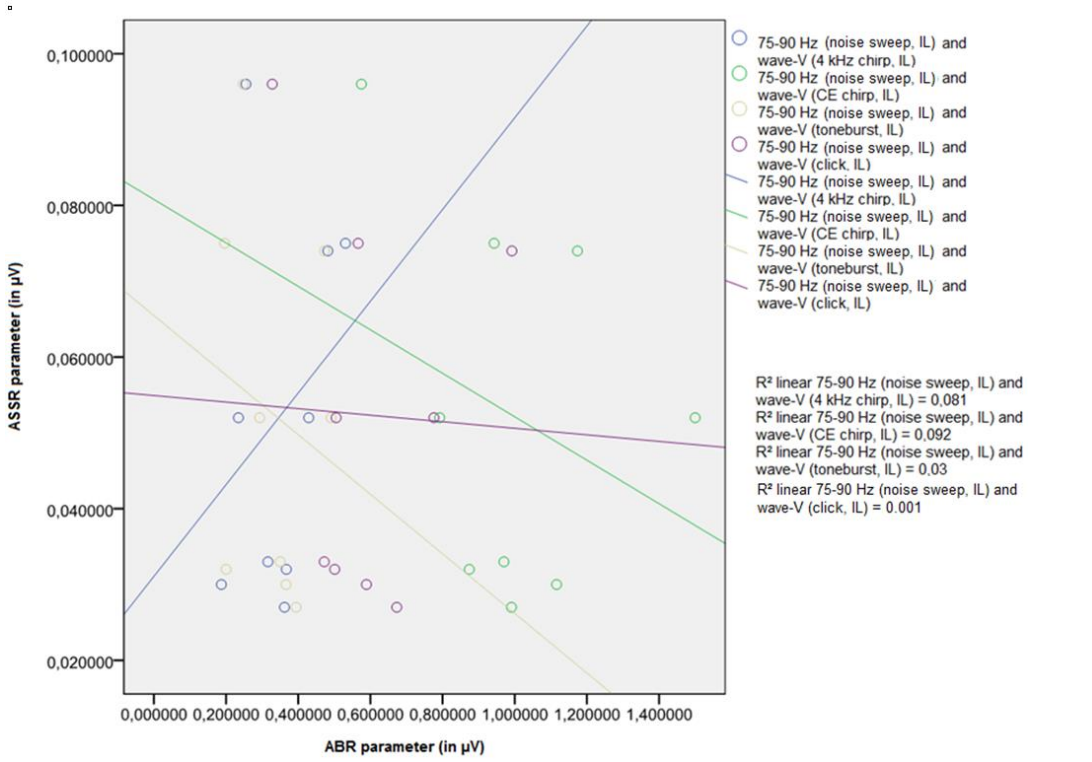
Stim.	Study	Differences				A wave I	SD	A wave V	SD
		Level	Electrode	Rate (Hz)	Other	(µV, p-t-p)		(µV, p-t-p)	
4 kHz	Stamper & Johnson (2014)	80 dB nHL	TM	11.3		0,739	0,316	0,324	0,116
TB		80 dB nHL	mastoid	11.3		0,377	0,135	0,395	0,131
TB	Yanz & Dodds (1985)	60 dB SL	mastoid	11.1	1 cycle of 3 kHz sinus	0,390		0,640	
		60 dB SL	in ear	11.1	1 cycle of 3 kHz sinus	0,520		0,550	
Click	Stamper & Johnson (2014)	80 dB nHL	TM	11.3		0,769	0,330	0,495	0,142
		80 dB nHL	mastoid	11.3		0,397	0,137	0,584	0,187
	Elberling & Don (2008)	60 dB nHL	mastoid	27	Rarefaction, ER-2 earphone			0,331	0,069
		50 dB nHL	mastoid	27	Rarefaction, ER-2 earphone			0,305	0,058
	Beattie & Lipp (1990)	75 dB SL		11.1		0,499	0,131	0,411	0,132
	Elberling et al. (2010)	60 dB nHL		27	ER-2			0,407	0,091
		40 dB nHL		27	ER-2			0,368	0,092
	Musiek et al. (1986) and Musiek et al. (1984)	80 dB nHL		11.3/15.3	TDH-39	0,300	0,100	0,450	0,110
	Elberling et al. (2007)	50 dB nHL		90				0,340	
	Elberling, Don et al. (2012)	50 dB nHL		27.1				0,351	0,081
	Kristensen & Elberling (2012)	60 dB nHL		27.1				0,401	0,079
		40 dB nHL		27.1				0,317	0,091
	Elberling, Kristensen et al. (2012)	60 dB nHL		27.1				0,389	0,091
		40 dB nHL		27.1				0,309	0,078
	Bauch & Olsen (1990)	85 dB nHL		11.1	Rarefaction	0,338	0,168	0,390	0,190
Chirp	Elberling et al. (2007)	50 dB nHL		90	Don chirp			0,820	
		60 dB nHL		27	ER-2, 200-10000 Hz			0,501	0,104
		50 dB nHL		27	ER-2, 200-10000 Hz			0,531	0,132
	Elberling et al. (2010)	60 dB nHL		27	k= 0.1083, d=0.4583, 20-10000 Hz, ER-2			0,596	0,118

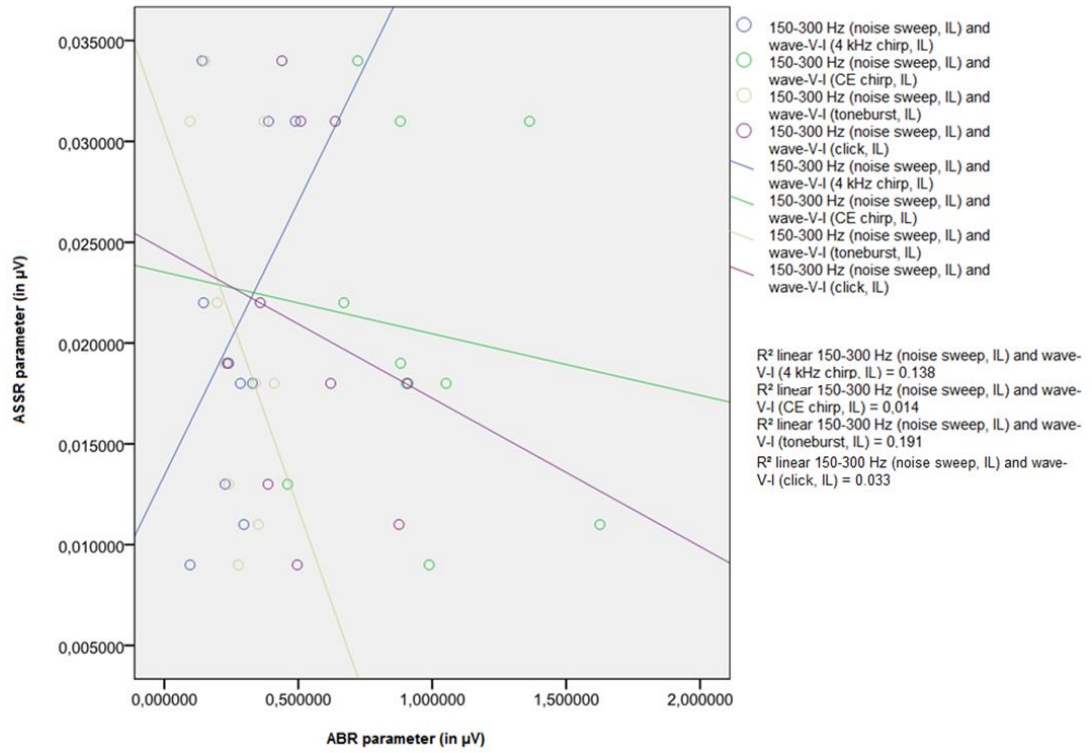
		40 dB nHL	27	k= 0.1083, d=0.4583, 20-10000 Hz, ER-2	0,645	0,079
	Elberling, Don et al. (2012)	50 dB nHL	27.1	LS-chirp	0,575	0,109
CE-	Kristensen & Elberling	60 dB nHL	27.1		0,574	0,167
chirp	(2012)	40 dB nHL	27.1		0,531	0,102
	Elberling, Kristensen et al.	60 dB nHL	27.1		0,525	0,191
	(2012)	40 dB nHL	27.1		0,495	0,141

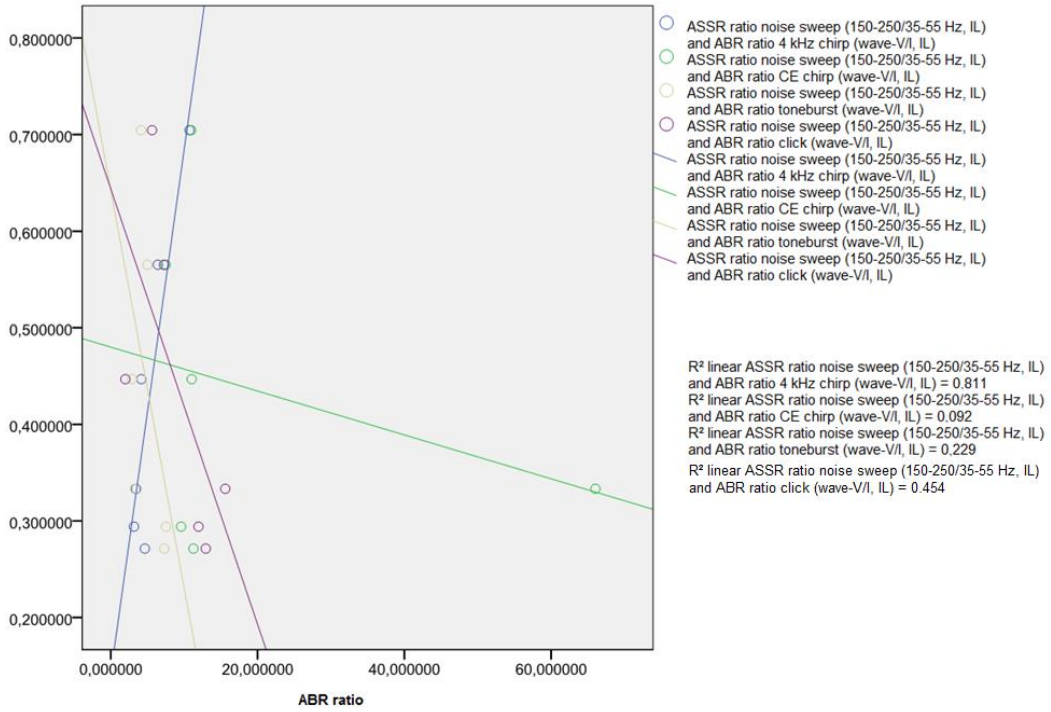
Appendix L. *Scatterplots of expected correlations between ASSR (y-axis) and ABR (x-axis) parameters.*






ASSR parameter (in µV)
0,100000
0,080000
0,060000
0,040000
0,020000
0,000000 0,200000 0,400000 0,600000 0,800000 1,000000 1,200000 1,400000
ABR parameter (in µV)
75-90 Hz (noise sweep, IL) and wave-V (4 kHz chirp, IL)
75-90 Hz (noise sweep, IL) and wave-V (CE chirp, IL)
75-90 Hz (noise sweep, IL) and wave-V (toneburst, IL)
75-90 Hz (noise sweep, IL) and wave-V (click, IL)
75-90 Hz (noise sweep, IL) and wave-V (4 kHz chirp, IL)
75-90 Hz (noise sweep, IL) and wave-V (CE chirp, IL)
75-90 Hz (noise sweep, IL) and wave-V (toneburst, IL)
75-90 Hz (noise sweep, IL) and wave-V (click, IL)
R² linear 75-90 Hz (noise sweep, IL) and wave-V (4 kHz chirp, IL) = 0,081
R² linear 75-90 Hz (noise sweep, IL) and wave-V (CE chirp, IL) = 0,092
R² linear 75-90 Hz (noise sweep, IL) and wave-V (toneburst, IL) = 0,03
R² linear 75-90 Hz (noise sweep, IL) and wave-V (click, IL) = 0.001


ASSR parameter (in µV)
0,035000
0,030000
0,025000
0,020000
0,015000
0,010000
0,005000
0,000000 0,500000 1,000000 1,500000 2,000000
ABR parameter (in µV)
150-300 Hz (noise sweep, IL) and wave-V-I (4 kHz chirp, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (CE chirp, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (toneburst, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (click, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (4 kHz chirp, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (CE chirp, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (toneburst, IL)
150-300 Hz (noise sweep, IL) and wave-V-I (click, IL)
R² linear 150-300 Hz (noise sweep, IL) and wave-V-I (4 kHz chirp, IL) = 0.138
R² linear 150-300 Hz (noise sweep, IL) and wave-V-I (CE chirp, IL) = 0,014
R² linear 150-300 Hz (noise sweep, IL) and wave-V-I (toneburst, IL) = 0.191
R² linear 150-300 Hz (noise sweep, IL) and wave-V-I (click, IL) = 0.033


0,800000
0,700000
0,600000
0,500000
0,400000
0,300000
0,200000
0,000000
20,000000
40,000000
60,000000
ABR ratio
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio 4 kHz chirp (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio CE chirp (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio toneburst (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio click (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio 4 kHz chirp (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio CE chirp (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio toneburst (wave-V/I, IL)
ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio click (wave-V/I, IL)
R² linear ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio 4 kHz chirp (wave-V/I, IL) = 0.811
R² linear ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio CE chirp (wave-V/I, IL) = 0.092
R² linear ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio toneburst (wave-V/I, IL) = 0.229
R² linear ASSR ratio noise sweep (150-250/35-55 Hz, IL) and ABR ratio click (wave-V/I, IL) = 0.454

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