University of Southampton

Faculty of Engineering and Physical Sciences

Institute of Sound and Vibration Research

Investigating measures of high-frequency hearing function and the effects of noise exposure

by

Hind Maher Alenzi

Thesis for the degree of Doctor of Philosophy

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Abstract

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Many young adults engage in loud activities, which can cause noise-induced hearing loss (NIHL). Some studies suggest that NIHL and age-related hearing loss (ARHL) lead to relatively rapid shifts in the hearing threshold level (HTL) of the extended high frequency (EHF) range (> 8 kHz). It has been hypothesised that NIHL may first present with HTL elevations in the EHF range before the conventional audiometric frequency (CAF) range of 0.25 to 8 kHz. In this research, three studies were reported related to hearing in the EHF region.

Study 1A aimed to assess the effect of noise exposure on different measures of EHF hearing. It also aims to establish which parameters of EHF-OAEs can derive the highest signal amplitudes and signal to noise ratio (SNR). Finally, it aims to determine which EHF-OAEs better predict EHF-HTL. Data were collected from 58 young adults (18-34 years) with normal hearing in CAF-range, using EHF pure tone audiometry (EHF-PTA), transient evoked otoacoustic emissions OAE (EHF-TEOAE) recorded with double-evoked (DE) using high-pass filter (HPF) and toneburst (TB 10 kHz) stimulus waveform, as well as distortion product OAE (EHF-DPOAE) recorded with (70/70) and (65/55) stimulus level paradigm. Noise exposure history was quantified using noise exposure structured interview (NESI). It was found that EHF-HTL showed more association with noise exposure than CAF-HTL. The current study also showed measuring EHF-DPOAEs using (70/70) dB SPL can evoked greater amplitude for the EHF-range. But when assessing which EHF-OAEs measurement can predict EHF-HTL it was found that EHF-DPOAEs recorded with (65/55) dB SPL predict EHF-HTL more strongly than EHF-DPOAEs using (70/70). It was also found that EHF-TEOAEs (TB and HPF) might predict EHF-HTL equally.

Study 1B aimed to observe changes in EHF measurement in association with noise exposure over 16 months. It also aims to assess the correlation between EHF-OAEs and EHF-HTL. Three visits

were conducted, each separated by 6–8 months (baseline [n = 58], phase 1 [n = 43], and phase 2 [n = 26]). The results showed no discernible hearing changes over 8–16 months, except for CAF-HTL and EHF-HTL over 16 months, due to noise exposure but the pattern of results was complex, and it is speculated that they may have been influenced by possible calibration drift over the duration of the study.

Study 2 aimed to assess whether the correlation between audiogram fine structure (AFS) and normal HTL and TEOAEs in the EHF range would be similar to that seen in the CAF range. Data for Studies 2 and 3 were collected simultaneously from 28 subjects. The results did not show the correlations in the EHF-range that have been reported in the CAF range, which may be due to weaker interference between forward and reverse cochlear travelling waves in the most basal region (EHF) compared to most apical areas (CAF) or a difference in cochlear mechanical properties.

Study 3 aimed to establish whether evoking the novel use of EHF-TEOAEs with maximum length sequences (MLS) or DE paradigm can show greater SNR. The SNR from EHF-TEOAE recorded using DE-paradigm were statistical significantly better than the SNR from EHF-TEOAE using MLS. In addition, only the EHF-TEOAE recorded using DE technique in the 9.4-kHz ½-octave band achieved an SNR that would be clinically useful (> 6 dB SNR).

Table of Contents

Table of Tables

Table of Figures

Research Thesis: Declaration of Authorship

Print name: Hind Maher Alenzi

Title of thesis: Investigating measures of high-frequency hearing function and noise exposure

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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- Alenzi, H. M., and Lineton B., 2021. Transient otoacoustic emissions and audiogram fine structure in the extended high-frequency region. *International Journal of Audiology.*

Poster presentations:

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- British Society of Audiology (BSA) annual e-Conference (2019).
- Human Sciences Group (University of Southampton) research away day (2018).
- Ear and Hear in Southampton (University of Southampton) Audiology and Audio conference (2022).
- Inner Ear Biology (IEB) Symposium 56th (2019).

Oral presentations:

- Signal Processing, Audio and Hearing Group (University of Southampton) (2020)

Signature: Hind Maher Alenzi .... Date: 11/07/2022 ....

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Abbreviations

ARHL	Age-related hearing loss
AFS	Audiogram fine structure
B&K	Bruel and Kjaer
BM	Basilar membrane
CF	Characteristic frequency
CAF	Conventional audiometric frequency
CAF-DPOAE	Conventional audiometric frequency-distortion product otoacoustic emission
CAF-HTL	Conventional audiometric frequency-hearing threshold level
CAF-PTA	Conventional audiometric frequency-pure tone audiometry
CAF-TEOAE	Conventional audiometric frequency- transient evoked otoacoustic emission
DE	Double evoked
DPOAE	Distortion product otoacoustic emission
EAC	External auditory canal
EHF	Extended high frequency
EHF-DPOAE	Extended high frequency-distortion product otoacoustic emission
EHF HTL	Extended high frequency-hearing threshold level
EHF-OAE	Extended high frequency- otoacoustic emission
EHF-PTA	Extended high frequency- pure tone audiometry
EHF-TEOAE	Extended high frequency-transient evoked otoacoustic emission
EPL	Emitted pressure level
FTC	Frequency-threshold curve
F/U	Follow up
FPL	Forward pressure level
HCs	Hair cells
HL	Hearing loss
HTL	Hearing threshold level
IE	Inner ear
IHCs	Inner hair cells
LMM	Linear mixed model
ME	Middle ear
NESI	Noise exposure structured interview
NIHL	Noise induce hearing loss
NIPTS	Noise induce permanent threshold shift

OAEs	Otoacoustic emissions
OE	Outer ear
OHCs	Outer hair cells
OW	Oval window
PLD	Personal listening device
PTA	Pure tone audiometry
PTC	Psychophysical tuning curves
PTS	Permanent threshold shift
RETSPLs	Reference equivalent threshold sound pressure levels
RDNL	Rate drive nonlinear
RQ	Research Question
ROS	Reactive oxygen species
SD	Standard deviation
SFOAE	Stimulus frequency evoked otoacoustic emission
SLC	Sound level calibrator
SNHL	Sensorineural hearing loss
SNR	Signal to noise ratio
SOAE	Spontaneous otoacoustic emissions
SPL	Sound pressure level
TEOAE	Transient evoked otoacoustic emission
TTS	Temporary threshold shift
TW	Travelling wave

Chapter 1 Introduction

1.1 Background, Rationale and Thesis Aims

Sensorineural hearing loss (SNHL) is the most common type of hearing loss (HL) in adults. It occurs when there is damage to the cochlea and/or the auditory nerve, and is irreversible (Daniel, 2007; Katz, 2015). This type of hearing loss goes beyond the effect on hearing ability, it also affects the clarity of speech signals, resulting in the unclear perception of speech (Plomp, 1978). SNHL can be congenital, where the subject is born with a hearing defect, or it can be acquired either with age (age-related hearing loss, ARHL), noise exposure (noise-induced hearing loss, NIHL), or from the use of ototoxic drugs that can harm hearing.

NIHL is a common type of HL (Rabinowitz, 2000; Mehrparvar et al., 2014) that can be almost completely prevented by reducing exposure to loud sounds. Social noise exposure is on the rise, influenced by changes in the leisure and relaxation activities that are popular among young adults (Smith et al., 2000), as well as by the increased use of personal listening devices (PLD) at high sound levels. A diagnosis of NIHL is based on a notch between 3 and 6 kHz in a Conventional audiometric frequency (CAF) audiogram, along with a reported history of noise exposure. There is considerable variation between individuals in their susceptibility to noise exposure harm, and this can also be influenced by factors such as heredity, diabetes, and life-style choices such as smoking (Sliwinska-Kowalska and Pawelczyk, 2013). It has been speculated that the basal end of the cochlea (tuned to Extended high frequency [EHF]) is more affected by aging, noise exposure, and ototoxic drugs than the more apical regions, resulting in a rapid increase in extended high frequency-hearing threshold level (EHF-HTL) (Ahmed et al., 2001; Wang et al., 2000; Knight et al., 2007). This is discussed in more detail in Chapter 2.

EHF measurements could be a promising tool for monitoring hearing ability for noise exposed individuals, but this area is not yet fully understood. There is, to date, little research on the relationship between EHF-HTL, extended high frequency- otoacoustic emission (EHF-OAEs) and noise exposure, and little is known about the behaviour of the cochlear mechanism at EHF range. Moreover, methods for evoking extended high frequency- transient evoked otoacoustic emission (EHF-TEOAEs) are currently limited, and thus, novel measurements for EHF-TEOAEs are needed. At the same time, there is a lack of research on the impact of noise exposure on EHFs over time, and so a longitudinal study to observe changes in EHF hearing is needed. In addition, there is relatively little research investigating the use of extended high frequency-distortion product otoacoustic emission (EHF-DPOAEs) and EHF-TEOAEs in measuring the effects of noise exposure.

Accordingly, this research project conducted three separate studies to investigate measurements relating to hearing in the EHF range, as outlined below.

There are many things that are not known about the EHF hearing; therefore, the main aim of this study is to understand the EHF function and whether the cochlear physiology for OAE is similar to that found in CAF range. All the specific aims for the three studies are drawn from the aim to better understand the EHF-hearing function. For the first study, the main aim is to assess the sensitivity of EHF hearing to noise exposure and whether the EHF hearing measurements are more sensitive to noise exposure than CAF range. In addition, it also aims to assess whether there are changes in EHF hearing measurements due to cumulative noise exposure and age over a period of 16 months. The aim of study 3 is to use different methods (i.e. DE and RDNL) for evoking EHF-TEOAEs and to determine which one evoked higher SNR. The plan was to conduct this study before study 1 to decide whether to use DE or RDNL for study 1. However, due to several reasons including time limitations, issues encountered with equipment, and equipment set up, the study took longer than expected. Therefore, to avoid any delay that might not allow the accomplishment of the longitudinal study, it became a priority to allow sufficient time for F/U sessions. It is worth mentioning that the results from study 3 did not affect the decision to use DE parameter in the longitudinal study, as it was found that DE evoked greater TEOAEs SNR than RDNL.

One of the aims of the thesis was to better understand what determines EHF HTLs and OAEs, and how they differ from HTLs and OAEs at CAFs. Therefore, study 2 aims to assess the cochlear mechanical behaviour and whether it is similar to what was seen in CAF range in terms of correlation between AFS ripple depth and both HTL-PTA and TEOAS at EHFs.

Study 1

Study 1 consists of two parts, Study 1A, the cross-sectional study (Chapter 3) and Study 1B, the longitudinal study (Chapter 4). The main aim of Study 1 was to investigate the effect of noise exposure on young adults' hearing, and to assess whether the effect of noise exposure is greater on EHF measurements of HTL, TEOAEs, and DPOAEs than CAF measurements. The motivation behind this was the likely involvement of this population in loud, noisy activities such as nightclubs, sporting events, and use of personal listening devices (PLD) (Smith et al., 2000). According to previous literature, EHF-HTL measurements can detect the early signs of changes in hearing due to noise exposure better than CAF-HTL measurements, and so this study aims to assess the effects of noise exposure on EHF hearing (Ahmed et al., 2001; Mehrparvar et al., 2014). It has also been suggested that early changes in hearing due to noise can be detected with OAEs, and so, accordingly, EHF measurements were conducted for TEOAEs and DPOAEs. EHF-OAEs are not often used to assess hearing.

The longitudinal study 1B was carried out to address the current lack of research into monitoring changes in EHF hearing over time. The aims and research questions of Chapters 3 and 4 are listed in Table 1.1 below.

1.1.1 Study 2

This study is covered in Chapter 5. The aim and research questions of this study are detailed in Table 1.1. The research aim was to test the assumption that correlations relating to cochlear mechanical behaviour found in the CAF range (Kapadia and Lutman, 1999) are also found in the EHF range. The theory proposes that the reflection of travelling waves (TW) results in both TEOAEs and audiogram fine structure (AFS), and it has been suggested by previous research that the AFS and TEOAE amplitudes correlate in the CAF region. However, few studies have investigated this correlation in the EHF-region.

1.1.1.1 The impact of COVID restrictions

The longitudinal study 1B, aims to investigate changes in EHF hearing over 2 years. But due to covid and other reasons related to equipment set up, the plan was changed to collecting data for 16 months instead of 2 years. In addition, due to covid lockdown restrictions, I had to cancel the scheduled F/U for 12 participants, which led to a smaller sample size than desired, with only 26 subjects completing all the 3 visits. Even after the wave of covid restrictions, it was difficult to track the participants for further F/U as almost all of them are students who have left Southampton, either due to completion of their studies or working from home arrangements.

1.1.2 Study 3

This study is presented in Chapter 6. TEOAEs are not often measured in the EHF region, due to the contamination of early latency (where EHF-OAE signals are recorded) with stimulus artifact. Therefore, potential methods for measuring EHF-TEOAEs need to be investigated. The possibility of eliminating the stimulus artifact was addressed in this study by using novel stimulus paradigms to assess EHF-TEOAEs. The double-evoked (DE) paradigm was used to provoke signals at the early latency of OAEs (with eliminated stimulus artifact), which are from the basal part of the cochlea. As well, DE using the rate-derived non-linear method (RDNL) may effectively move the stimulus artifact from the OAEs response. The aims and research questions for Study 3 are shown in Table 1.1.

Table 1.1: Research aims and questions of each chapter

Chapter	Aims	Research Questions
Chapter 3: Study 1A (cross-sectional data)	1. To assess the sensitivity of CAF and EHF hearing measurements to the effects of noise exposure in young adults, as assessed by the NESI[1] questionnaire. The measurements used are HTLs and the amplitudes and SNRs of DPOAEs and TEOAEs.	1. Do hearing measurements show greater sensitivity to NESI score at EHFs than at CAFs when the NESI score is treated as a continuous variable? 2. Do hearing measurements show greater dependence on NESI score at EHFs than at CAFs when the NESI score is used to define two noise exposure groups (low- NESI groups and high- NESI groups).
	2. To assess which parameters of EHF-TEOAEs and EHF-DPOAEs lead to the highest signal amplitudes and highest SNRs and therefore may be optimal for clinical applications.	1. Which stimulus levels, 65/55 or 70/70[2], are more useful in evoking better amplitudes and SNRs for EHF DPOAEs? 2. Which stimulus condition, HPF click or TB (10kHz) [3], is more useful in evoking better amplitudes and SNRs for EHF-TEOAEs?
	3. To assess how well OAE measurements predict EHF-HTLs. For example, when cochlear damage (either age or noise) was indicated by EHF-HTL, which OAEs can predict this damage, i.e. which are most strongly correlated with EHF-HTL?	1. How strongly do different EHF measurements correlate with each other, and with measurements in the CAF range? Specifically, what is the bivariate correlation matrix between HTLs, DPOAEs and TEOAEs, with these measurements averaged separately over the CAF and EHF ranges?
Chapter 4: Study 1B (longitudinal data)	4. To determine whether changes in hearing status at EHFs due to aging and noise exposure can be detected over a period of 06 to 16 months, using EHFs HTL and EHFs OAEs.	1. Can increases in EHF-HTL be detected in a group of young adults with a range of noise exposures over a 06 to 16-month period? 2. Can increases in EHF-DPOAEs and EHF-TEOAEs be detected in a group of young adults with a range of noise exposures over a 06 to 16-month period? 3. Are changes in EHFs HTLs and EHFs OAEs over a 06 to 16-month period related to NESI score over the same period? 4. How well do changes in the amplitude of EHFs OAE predict changes in EHF-HTL?
Chapter 5: Study 2	1. To assess whether TW reflection mechanisms in the EHF range show similar properties to those in the CAF range.	1. Was there a correlation between AFS ripple depth and HTL-PTA at EHFs? 2. Was there a correlation between AFS ripple depth and TEOAE amplitude?

		3. Does the AFS show distinctive regular spectral periodicity at the expected spectral interval?
Chapter 6: Study 3	1. To assess whether the RDNL paradigm provides benefits to EHF-TEOAE measurements over the DE paradigm.	1. Do RDNL and DE paradigms give similar waveforms? 2. Is the SNR estimated for RDNL better than that for the DE paradigm for the same recording time?

NESI stands for Noise Exposure Structured Interview[1].
EHF-DPOAEs were measured using low- and high-level stimulus levels, termed here the “70/70” and “65/55”[2].
EHF-TEOAEs were measured using two stimulus paradigms, termed here the “HPF” and “TB” paradigms[3].

1.2 Overview of thesis structure

This research consists of three main parts, corresponding to the three studies of EHF hearing (Figure 1.1). The first part investigates the relationship of EHF hearing to noise exposure and aging. To achieve this goal, the longitudinal study 1B was designed to observe changes in EHF hearing due to noise exposure over a period of time (see Chapter 4). The cross-sectional study 1A was conducted to obtain baseline data to assess the impact of noise exposure on EHF hearing (Chapter 3). The second part, Study 2, aims to understand cochlear physiology in the EHF range with regard to the generation mechanisms of OAEs and AFS via TW reflection, as seen in the CAF range (Chapter 5). Study 2 investigates whether the correlations between EHF measurements in normal hearing subjects are similar to those between CAF measurements, as reported in the literature. The third part, Study 3, covered in Chapter 6, aims to investigate potential measurement techniques for EHF TEOAEs, i.e. DE and RDNL, to determine which can evoke greater signal amplitude and greater SNR.

Figure 1.1 shows the schematic diagram for the research project.

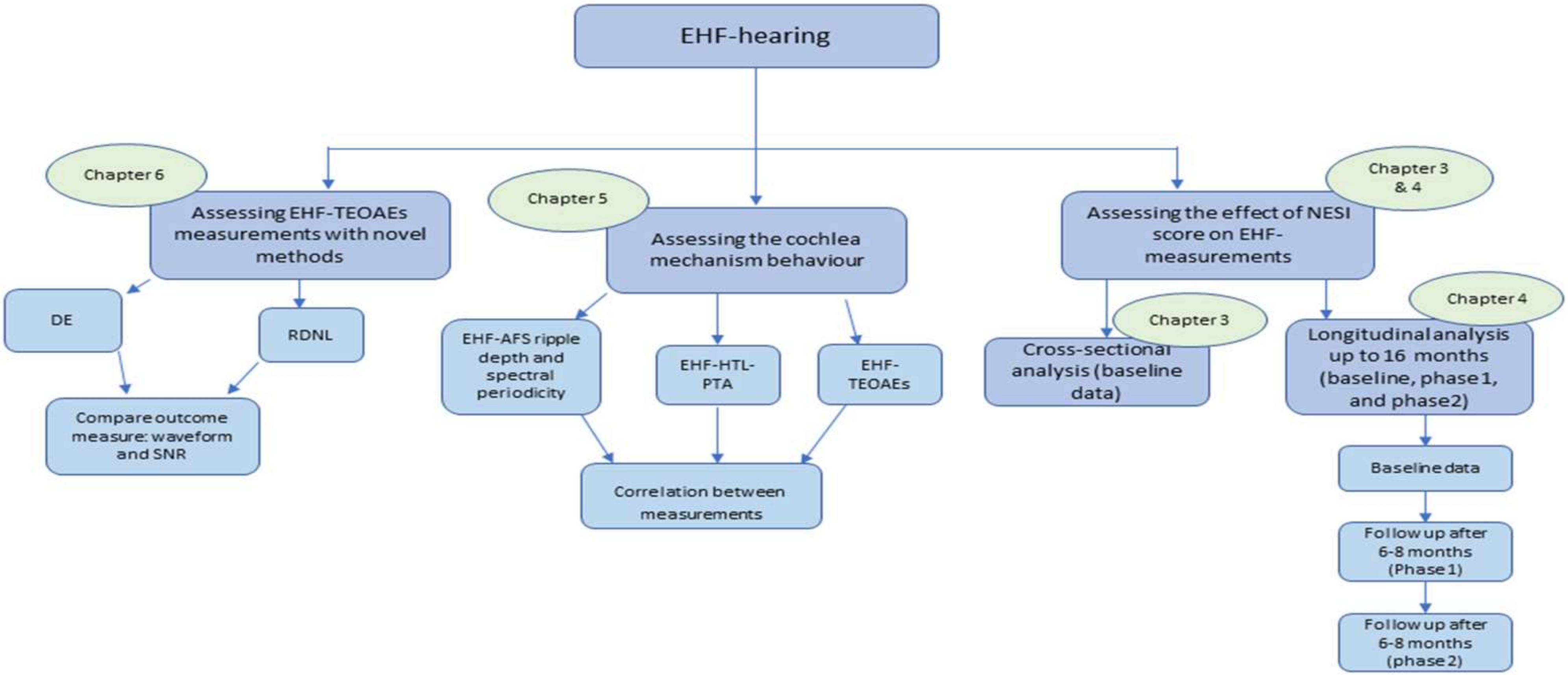


Figure 1.1: Schematic diagram of the research project

The following paragraphs provide an overview of each chapter.

Chapter 2: Introduction to Hearing in the EHF range

This chapter provides the knowledge necessary to understand the content of this thesis and also constitutes the Literature Review. It introduces contributing factors such as the aging process, noise exposure, and other environmental factors that affect EHF hearing, as well as the condition of NIHL and its impact on hearing in general. The chapter also describes how the SPLs of hearing for otologically normal ears increase sharply with EHF and looks at calibration methods that can overcome issues regarding the EAC and EHF signals that result in intra- and inter-subject variability, and what method was used in the current study. An overview of hidden hearing loss is also given.

Chapter 3: Relationship between high frequency hearing and noise exposure (Study 1A)

Chapter 3 covers Study 1A, which assesses the relationship between noise exposure and objective measures of hearing of both CAFs and EHFs using cross-sectional data. Data was collected from 58 young adults using HTL, TEOAEs, and DPOAEs in both the CAF and EHF ranges. Each participant's lifetime noise exposure measurement was quantified using NESI scores. The NESI score is used to subjectively estimate the cumulative life-time noise exposure. Part of this questionnaire included some elements that were originally developed for a Health and Safety Executive questionnaire (Lutman et al., 2008). However, this questionnaire was adjusted by Guest et al. (2018) to allow it use for recreational noise exposure, along with occupational noise exposure. The reasons for using this questionnaire rather than others were that it is easy to use, and it is flexible, as it allows the user to quantify changes in exposure habits over time. Moreover, part of this questionnaire was validated and extend to add further details, as mentioned in chapter 3.

The results show that noise exposure affects HTL at both CAF and EHF regions, and that HTLs are affected more at EHFs that at CAFs. In contrast, no effect on EHF-TEOAE and EHF-DPOAE amplitude and SNR was found due to noise exposure. Differences between groups showed no significant difference in EHF-measurements. EHF-DPOAEs showed greater amplitude and SNR from (70/70) and EHF-TEOAEs had greater amplitude and SNR from HPF. However, the EHF-DPOAEs (65/55) correlated more with EHF-HTL. Similar negative correlation was found between EHF-HTL and EHF-TEOAEs (HPF). A positive correlation was found between EHF-TEOAEs and EHF-DPOAEs.

The aim of study 3 is to use different methods (i.e. DE and RDNL) for evoking EHF-TEOAEs and determine which one evoked higher SNR. The plan was to conduct this study before study 1 to decide whether to use DE or RDNL. Nevertheless, due to several reasons including time limitations, issues encountered with equipment, and equipment set up took longer time than expected, there was a priority to start as soon as possible to allow sufficient time for F/U sessions. It is worth mentioning that the result from study 3 did not affect the decision to use DE parameter in the longitudinal study, as it was found that DE evoked greater TEOAEs SNR than RDNL.

Chapter 4: The longitudinal relationship between high frequency hearing and noise exposure (Study 1B)

This chapter covers the longitudinal study 1B, which aims to investigate changes in EHF hearing over a period of 16 months, using data collected over 3 time points. It is worth mentioning that difficulties were encountered in this study such as, there was a considerably higher drop-out rate from the study than had been anticipated, leading to a smaller sample size than desired with only 26 subjects completing all the 3 visits. In addition, follow-up was also hampered by the Covid restrictions.

It was found that over 16 months, HTL data showed statistically significant differences in the CAF range due to noise exposure or age, but pattern of results was complex. There were also statistically significant differences in the EHF range due to noise exposure, but again pattern of results was complex, and it is speculated that they may have been influenced possible calibration drift over the duration of the study. No changes after 16 months were seen for CAF and EHF using TEOAEs and DPOAEs. A positive correlation was found between EHF-TEOAEs and EHF-DPOAEs.

Chapter 5: Transient otoacoustic emissions and audiogram fine structure in the extended high-frequency region (Study 2)

This chapter starts by reviewing the current literature on cochlear mechanical properties found measuring AFS, TEOAEs, and PTA-HTL in the CAF range. The literature has reported a correlation between the AFS and both amplitudes of TEOAEs and overall manual HTLs. The aim of this chapter was to investigate whether similar cochlear mechanical behaviour was observed in the EHF region also, and to investigate whether a similar correlation was observed with EHF hearing. The study aims and research questions are listed in Table 1.1. Measurements of AFS, TEOAEs and manual HTLs were collected from 28 subjects. No significant correlation was observed between AFS and both TEOAEs and manual HTL in the EHF region. The findings did not show a similar correlation as seen for the CAF region, possibly because either the mechanism was weak or not present at the EHF. This study was published as an original article in the International Journal of Audiology (Appendix E). Note that in this chapter, the standard PTA will be referred to as manual PTA.

Chapter 6: Investigating the use of a rate-derived non-linear technique for acquiring TEOAEs in the extended high-frequency region (Study 3)

This chapter investigates the possibility of measuring EHF-TEOAEs using novel parameters (i.e. DE and RDNL) and establishes whether measuring EHF-TEOAEs using the RDNL method, which relies on maximum length sequences (MLS), can elicit greater amplitude and SNR than the current method used in our study: the DE. The study aims and research questions are listed in Table 1.1 Data for Studies 2 and 3 were collected at the same time from 28 subjects. Both DE and RDNL were able to measure amplitude and SNR. EHF-TEOAEs SNR of DE are greater than RDNL.

1.3 Contributions to knowledge

This thesis has made contributions towards the understanding of EHF hearing by assessing the cochlear mechanism function for that range, and novel measurement of EHF-TEOAEs, and by assessing how noise exposure can affect hearing in the EHF range at the baseline (cross-sectional analysis) and over time (longitudinal analysis). The contributions of the current thesis can be summarised in the following points.

- Noise exposure correlates with HTL more at EHF than CAF.
- The study assesses the relationship between noise exposure (assessed by the NESI score) and objective measures of hearing (assessed using HTLs, TEOAEs and DPOAEs), at both CAF and EHFs, in a cross-sectional study. The findings were broadly in agreement with previous studies that suggested that measurements in the EHF range may provide additional information about the effects of noise exposure on hearing status to that at CAFs, at least for HTL.
- The study assessed low (65/55) and high (70/70) stimulus levels in evoking EHF-DPOAEs. The findings revealed that high stimulus was more effective in evoking greater amplitude and SNR than low level, possibly because EHF signals require high stimulus levels in order to be triggered.
- Although the EHF-DPOAEs with (70/70) can evoke greater amplitudes than EHF-DPOAEs at (65/55), the EHF-DPOAEs using (65/55) stimulus was significantly more strongly correlated to EHF-HTLs, for both amplitude and SNR. This could imply that the EHF-DPOAES using (65/55) stimulus predicts EHF-HTLs more accurately than the evoked EHF-DPOAES using (70/70). It could be useful to use EHF-DPOAEs at (70/70) for monitoring changes in cochlear function in an individual ear over time, while the EHF-DPOAEs at (65/55) might be more useful in assessing cochlear function at a single point in time.
- The use of the high pass-filtered click (HPF) can be effective in evoking a genuine signal of EHF-TEOAEs, designed to evoke broad energy from the EHF, which can deliver more

stimulus energy in the EHF region than the standard rectangular default click, and it can reduce lower-frequency stimulus energy that may cause some suppression of EHF-responses, and increases the subjective loudness for the stimulus.

- The use of a tone burst stimulus centred at 10 kHz to evoke EHF TEOAE was compared to the HPF stimulus paradigm. While the tone-burst paradigm was effective in evoking genuine EHF-TEOAEs, it was found that the SNRs of these were not as great as the SNRs of EHF-TEOAEs evoked using the HPF stimulus paradigm, which is thus the preferred stimulus paradigm. The HPF stimulus led to a greater EHF-TEOAE SNR than did the tone-burst, and thus appears to be the preferred stimulus paradigm for evoked EHF-TEOAEs.
- This thesis contributes towards understanding the cochlear mechanisms of travelling wave amplification and reflection in the EHF-range. In contrast to the results of studies in the CAF range, the current study found no correlations between AFS and either HTL or TEOAEs amplitudes. It was also evident that the TEOAEs and AFS in the EHF were weaker than in the CAF range, and, when plotted on spectral periodicity distribution, no peak was discernible which indicated that the AFS showed no single dominant spectral spacing in the ripple pattern.

1.4 Research activities completed

❖ **Articles published in peer-reviewed journals**

- Transient otoacoustic emissions and audiogram fine structure in the extended high-frequency region. Published in *International Journal of Audiology*, February 2021. https://doi.org/10.1080/14992027.2021.1899313

❖ **Presentations at external conferences**

- *Investigating measures of high-frequency hearing function and noise-exposure in a longitudinal study.* Poster presentation at the Conference of the British Society of Audiology, 2019, Wolverhampton, UK.
- *Investigating OAEs and audiogram fine structure in the extended high-frequency region.* Poster presentation at the 56th Symposium of Inner Ear Biology, Italy, 2019.
- *Investigating measures of high-frequency hearing function and noise exposure in a longitudinal study.* Poster presentation at the BSA e-Conference, UK, 2019.
- *The effect of recreational noise exposure on hearing thresholds, TEOAEs, and DPOAE above 8 kHz.* Poster abstract submitted to Ear and Hear, September 2022.

❖ **Internal presentations (University of Southampton)**

- *Investigating measures of high-frequency hearing function and noise-exposure in a longitudinal study*. Oral presentation at ISVR, University of Southampton, 2020.

Chapter 2 Introduction to hearing in the EHF range

2.1 Physiology of the human ear

A sound initiates a series of processes in order to be heard. It starts with a sound wave that arises from an object that is vibrating in the medium of air. This sound wave travels across the different parts of the hearing system before it initiates neural signals and is perceived by the brain. The main parts are the outer ear (OE), the middle ear (ME), and the inner ear (IE), as outlined below in more detail.

2.1.1 Outer and middle ear

The OE consists of the pinna and the external auditory canal (EAC), the pinna is the visible part of the OE; it collects and modifies sounds which are then delivered to the EAC (Gelfand, 2016 p. 69). The EAC is a tube with a closed-end tympanic membrane and an open-end auricle. It is about 2.3 cm long in adults, and works as a quarter- and half-wavelength resonator. Sounds entering the EAC become amplified if they are close to the resonance frequency (Gelfand, 2016 p. 70). This allows the EAC to function as a band-pass filter, leaving low-frequency sounds unaffected but amplifying higher frequencies between 2 kHz and 5 kHz due to quarter-wave resonant frequencies (Gelfand, 2016 p. 70). The OE also has higher-frequency resonances, approximately at 8 kHz, due to half-wavelength resonant frequencies in the EAC, that affect sound transmission in both inward and outward directions (Charaziak and Shera, 2017). Further discussion can be found in Section 5.2.

The ME overcomes energy loss by acting as an acoustic transformer. The loss is prevented by overcoming impedance mismatch between two different mediums, the low impedance of the air-filled ME and the high impedance of the fluid-filled IE. The ME transmits acoustic signals and reduces sound energy loss that can occur due to impedance differences in these mediums. However, the efficiency of sound transmission by the ME is not equal across frequencies, as more energy can be transmitted for the lower than higher frequencies. It has been suggested, therefore, that the ME act as a band-pass filter with a broad bandwidth ranging from 0.5–5 kHz, and any sounds outside this frequency range are therefore attenuated (Moore, 2012 p. 24). In addition, at least for frequencies up to 10 kHz, reverse transmission of sound from the cochlea to the ear also reduces rapidly with frequencies above 5 kHz which affects otoacoustic emissions

(OAEs) (Puria, 2003). Hence it has been suggested that the ME transmission characteristic is one of the reasons why the EHF-HTL (expressed in dB SPL) increases rapidly with increasing frequency in normal hearing subjects; further discussion on the relationship between ME function and EHF hearing will be found later in this chapter (see Section 2.3.2.2). The tonotopicity of the cochlea is another theory that has been suggested to explain the rapid shift in the absolute threshold of EHFs; further information will be covered later in this chapter (Section 2.3.2.3).

2.1.2 Inner ear

The IE consists of the hearing organ (cochlea) and the balance organs. The cochlea is a fluid-filled coiled cavity. It is divided into two membranes horizontally, the Reissner's membrane and the basilar membrane (BM), forming three chambers: the scala vestibule, scala media, and scala tympani. The BM houses the organ of Corti, which contains the hair cells (HCs): inner hair cells (IHCs) and outer hair cells (OHCs).

Movement of the stapes against the oval window (OW) causes a disturbance of the cochlea fluid, forming a travelling wave (TW) that propagates along the BM. Each point on the BM is tuned to a specific frequency, which shows the greatest displacement at this particular frequency, known as the characteristic frequency (CF). The response then gradually decreases as it moves away from the CF. Low stimulus frequencies cause maximum displacement in the apical region of the cochlea, whereas the high frequencies are tuned in the basal region (Moore, 2012 p 25-27).

The cochlea acts as an auditory filter that enhances the signal close to the CF and attenuates frequencies not close to the CF on the BM, from the basal end to the apical end. Filters at the base have narrower relative bandwidth than at the apex, at least for stimulus frequencies up to 10–12 kHz (Moore, 2012 p39). At the apex, filters are low-frequency band-pass filters, while at the base they are high-frequency band-pass filters. Thus, a normal cochlea can be considered to be a large bank of filters which improve the function of signal perception (Robles and Ruggero, 2001; Moore, 2012).

Similarly, there is a neural response to frequencies in the auditory nerves. Nerve fibres act similarly to the BM in terms of tuning characteristics; each neuron of the auditory nerve has a threshold at CF; below this level the nerve does not respond, while above it there will be no changes in response as it has reached saturation level (Moore, 2012). In other words, the neurons will fire at a higher rate when the signal is at or near the CF, and for signals further away from the CF the firing rate will be lower (for a given stimulus intensity). The relationship between threshold and frequency is known as the frequency-threshold curve (FTC) or tuning curve. It can be also referred to as frequency selectivity. The tuning curve is sharply tuned at high frequencies and broader at lower frequencies. Damage to the IE HCs causes loss of the sharp tuning and results in wider auditory filters, which in turn leads to responses to wider frequency ranges rather than being specific to frequency. This may cause difficulties in understanding speech in complex situations, e.g. noisy backgrounds, such situations were observed with SNHL.

The tuning curve can be measured invasively in animal studies by inserting a microelectrode in the auditory nerve, but this is not possible for human subjects as such a procedure would be unethical.

One way of assessing the tuning curves in human studies is via the psychophysical tuning curve (PTC), which is based on subjective behavioural responses. The PTC was used to estimate the auditory filter at certain CFs, the most popular procedure being the masking method. In this method the signal is fixed at a low level, at about 10 dB SL, just above the threshold, and is masked by a narrow-band noise with the same centre frequency but using varying intensities. The lower level of masker is recorded, and the process is then repeated at different frequencies of the masker, after which the PTC can show the shape of the auditory filter of the CF, which is the same as the signal used. Yasin and Plack (2005) used PTCs at EHFs to indicate that the BM appears to have characteristic frequencies that extend at least to 17 kHz. Suggesting that a travelling wave with a envelope peaking at a point on the BM is generated by stimuli at least up to 17 kHz.

2.2 Damage in the auditory system

All parts of the hearing system function together in order to sustain normal hearing, and disturbance in one or more of the parts may result in HL. For example, SNHL results from any damage to the IE. SNHL is the most common type of HL in adults; it can be congenital, where the subject is born with a hearing impairment, or it can be acquired either with ARHL, NIHL or from the use of certain drugs. This research focuses on acquired SNHL, especially that caused by noise, discussed in more detail below

2.2.1 NIHL

Noise can be defined as “unwanted sound” (Katz, 2015). In the context of NIHL, noise is most often used to mean any sound at high level, e.g. music. Noise exposure can disturb the normal functioning of the hearing system by changing its structure and function. The magnitude of any hearing threshold level (HTL) shift as a result of noise exposure, and the degree of hearing recovery, both depend on exposure level, duration, frequency, and individual characteristics, e.g. genetic and environmental factors (Helzner et al., 2005; Bovo et al., 2007). NIHL includes more qualitative characteristics that might be associated with noise exposure, as in tinnitus, or difficulty in understanding speech in noise, for example, rather than being presented simply as a quantification of threshold shift due to noise exposure.

Changes in the auditory system due to noise exposure may be reflected in a threshold shift, which can be temporary (temporary threshold shift, TTS) or permanent (permanent threshold shift, PTS). TTS is fully or partially reversible, since hearing level can return to its baseline level (before noise exposure) over a period of time; the recovery may be fast, within minutes or hours, or it may be slow, lasting days (Liu et al., 2004; Ryan et al., 2016). This phenomenon is often reported after attending loud events such as rock concerts (Bogoch et al., 2005). With regular and prolonged exposure to loud noise the damage to the auditory structures, especially the sensory cells, can become irreversible and result in PTS.

Noise-induced changes in the inner ear may be diagnosed from a CAF-HTL notch between 3 kHz and 6 kHz in an audiogram, where there is an associated reported history of noise exposure (Nelson et al., 2005). The notch is thought to occur in this frequency range because the physical properties of sounds are influenced and boosted by the EAC resonating at frequencies between 2 kHz and 4 kHz. The exact frequency at which it resonates depends on the length and volume of the ear canal, as the resonance increases with a decrease in the length of the ear canal (Katz, 2015).

2.2.2 What is the threat of recreational noise to hearing health?

HL impacts the listener’s life by impairing communication skills, which increases social isolation and anxiety, and reduces self-esteem. It can also negatively affect their work environment as the loss can affect their interest in communicating with colleagues and may cause decreased productivity at work (WHO, 2017).

This research focuses on the effects of noise exposure in acquired SNHL, rather than any of the other factors, because first, it is the second most common type of HL in adults, and second, many younger people are interested in activities that expose them to intense sound (music and/or noise). Such activities include attending concerts, sporting events, and clubs, and using personal listening devices (including smartphones) that may involve headphones or ear buds. The risks will obviously depend not only on the level but also on the duration of the exposure, as the total amount of sound energy that the individual can be exposed to safely in a single day is thought to be roughly constant (e.g., ISO 1999, 2013; HSE, 2005). Noise-induced HL can be therefore prevented by limiting noise exposure and using hearing protection.

Exposure to sound energy of moderate volume over a long period of time can lead to a risk of HL similar to that from exposure to higher volumes for shorter durations. **Error! Reference source not found.** presents permissible noise exposure levels for workers that consider the dose of sound intensity in relation to a given duration of exposure (i.e. equivalent continuous SPL [LAeq, dB]). Guidance is similarly set by agencies such as the Centers for Disease Control and Prevention and the Health and Safety Executive (CDC, 1998; HSE, 2005). These levels are calculated for work settings but are extrapolated for recreational exposure by World Health Organization [1]. Young people might put their hearing at risk by engaging in such events that can exceed the permissible noise exposure levels. Balanay and Kearney (2015) reported that many students are interested in attending activities with high noise levels such as sporting events, clubs or discos, rock concerts. Lawn mowers and firearms also produce high noise levels.

Table 2.1: Permissible noise level exposure duration that no worker shall exceed

Duration of exposure	L_{Aeq} **dB**
24 hours	80
8 hours	85
2 hours 30 minutes	90
47 minutes	95
15 minutes	100
4 minutes	105
1 minute 30 seconds	110
28 seconds	115
9 seconds	120

Derived from (CDC,1998)

Such activities were reported to often exceed the standard allowed daily exposure level; for example, the SPL at a sporting events was as high as 100.7-104.1 dBA, with a maximum peak of 120 dBA recorded during goal scoring (Hodgetts and Liu., 2006). These were LAeq 3hr levels (i.e. LAeq over the 3 hours of a hockey match). These correspond to daily exposure levels, normalised to 8 hours of 96.4-99.8 dBA, compared to the maximum permissible level of 85 dBA in **Error! Reference source not found.**.

Noise exposure from any source for a given intensity and duration will almost certainly have the same effect on the cochlea, therefore, in order to prevent hearing damage, the limits of exposure to sound have been established for both work and recreational exposure, with safe listening levels dependent on the intensity of sounds and the listening duration. In addition, unsafe levels of

[1] World Health Organization (WHO) was established in 1948 and is a United Nations agency that aims to promote health.

sound can come from personal listening devices (PLDs), which are now widely available. The easy accessibility of PLDs has meant that their use has increased, and users frequently listen to music and sounds at a high level over a long period of time (Portnuff et al., 2011). It has been found that many young adults expose themselves to unsafe loud sounds via PLDs (SCENHIHR 2008). Vogel et al. (2009) reported that 90% of 1,687 high school students were frequent users of PLDs, with 26% of them using their device for more than three hours a day and about half listening to sounds at the maximum output levels of their device. The range of maximum output level depends on the manufacturer and the headphones. The free-field equivalent LAeq at maximum volume output level ranged between 91 dBA and 121 dBA, with higher sound levels obtained through smaller headphones, such as insert phones (Fligor and Cox, 2004; Breinbauer et al., 2012). Studies on preferred PLD listening levels have reported that most adolescents raise the volume to over 85 dBA in silent background conditions, and this level may be increased in noisy situations (Hodgetts and Liu, 2006; Breinbauer et al., 2012). Therefore, the risks of these behaviours to listeners' hearing should be considered, and caution should be exercised to prevent any damage to hearing.

It has been reported by the Centers for Disease Control and Prevention (CDC, 2016) that listeners who suffer from even a small degree of hearing impairment can encounter difficulties in speech and language comprehension, communication, education, and social activities. It is also worth highlighting that there is a large inter-subject variability in the degree of NIHL (quantified by the noise-induced permanent threshold shift, NIPTS) for a given noise exposure for reasons that are not well understood (possibly genetic, or interactions with other factors such as smoking, or other diseases). The distribution of NIPTS across noise-exposed individuals for a given LAeq exposure duration can be estimated from ISO 1999, for audiometric frequencies up to 6 kHz (ISO 1999 2013). For example, with a daily exposure level of 90 dB A for 10 years, the range in the NIPTS of the 10–90 percentiles at 4 kHz varies from 7 to 15 dB.

2.3 Hearing evaluation

Hearing function is assessed both by objective testing such as auditory evoked potentials, otoacoustic emissions (OAE), and acoustic immittance testing, and subjective measurements such as pure tone audiometry (PTA) and speech audiometry.

PTA can be performed to detect the lowest sound pressure that a person can hear, known as the HTL. OAEs were defined by Kemp (1978) as low intensity sounds that are generated from normal functioning OHCs. These can be recorded by placing a probe in the external ear canal. Normal OAEs do not guarantee normal hearing, however, because this technique assesses the auditory pathway up to the OHCs in the cochlea, and does not provide any information about the integrity of retro-cochlear structures such as the auditory nerve. It has been well established that damage to the OHCs may be associated with a reduction in the OAEs (Brown et al., 1989).

Evoked OAEs reflect the function of the OHCs, and can be a valuable test for detecting preclinical NIHL that may be missed by CAF-PTA (Hotz et al., 1992). The clinical use of OAEs is mainly performed by transient evoked otoacoustic emissions (TEOAEs) or distortion product otoacoustic emissions (DPOAEs). Both are elicited in response to an external stimulus (Katz, 2015).

2.3.1 Frequency range in hearing and EHF

Hearing ability is often measured at CAF-range (0.25-8 kHz). Frequencies above 8 kHz are commonly referred to as EHFs and are not often tested clinically, despite the literature suggesting that the normal human auditory system has the ability to hear from approximately 20–20000 Hz (Fausti et al., 1981; Katz, 2015). The reason for testing the CAF-HTL is that this range of frequencies is important for speech intelligibility, as many speech cues are in this range (French and Steinberg, 1947). The predominance of speech cues in frequencies of < 8 kHz does not mean that there is no valuable information at EHFs for speech understanding. Previous studies have suggested that EHF energy may include information that is useful in identifying some speech sounds (e.g. fricatives) and contributes to speech perception to some extent, especially in difficult situations such as noisy restaurants (Best et al., 2005; Zadeh et al., 2019; Monson et al., 2014). EHFs might be important for speech perception.

The HTL at the EHFs were reported to show more inter and intra-subject variability than in the CAF range. Ahmed et al. (2001) reported that intra-subject variation was slightly greater at EHFs, while inter-subject variability at EHFs is considerably greater than at CAFs, but the variability is not so high as to make the measurements unusable for HTL. Similarly, Schmuziger et al. (2004) reported test-retest repeatability on healthy otological individuals at CAFs and EHFs. Both studies agreed that EHF-HTL could be reliable in monitoring hearing changes over time.

There is variability between the HTL of EHF and CAF range. The EHF intra-subject and inter-subject variability are higher compared to the CAF variability. For the intra-subject variability, the CAF-HTL shows variability of < 5 dB. Schmuziger et al. (2004) found test-retest errors were somewhat worse for EHF-HTL compared to CAF. Most HTL test-retest errors of about 99 % were ≤ 10 dB and many errors were around 88 %, equating to < 5 db. The variability was low enough to make the measurements usable.

Even among normal hearing subjects in the CAF-HTL, inter-subject variability in EHF HTLs can be high (Lee et al., 2012; Rodriguez Valiente et al., 2014). Previous studies reported that the standard deviation across subjects increased with increasing frequency. For example, the variation at 16 kHz was about 21-28 dB, which is about three times greater than the SD at 1 kHz.

The current study examines the significance of EHF measurements for the following reasons. First, normal hearing can extend to at least 20 kHz; second, valuable information can be provided by EHF sound, as it can assist localization and speech perception; third, due to the repeatability and reliability of EHF-HTL, EHF measurements may be effective in audiological diagnosis and health surveillance (e.g. regular monitoring in an industrial setting).

2.3.2 The steep rise in the minimum audible pressure with frequency in the EHF-region

When hearing threshold levels expressed in dB SPL are plotted against frequency (i.e. the minimum audible field), the curve shows a steeply rising threshold between 8 and 20 kHz, indicating a worsening hearing sensitivity at EHFs (Ashihara, 2007), this is also seen in RETSPL[2] (ISO 389-5:2006). Potential contributions to this curve are discussed in the following sections.

2.3.2.1 EAC characteristics

As mentioned earlier, the EAC works as an auditory filter (Section 2.1.1); the resonance of EAC can boost a certain frequency range (2–5 kHz). When sounds enter the EAC they are not fully transferred to the cochlea, as some energy will pass through the TM and some will be reflected to the EAC. The reflected energy will interact with the inward coming sound wave, resulting in the production of a standing wave. At a certain point in the wave there are pressure maxima and minima at EAC (Stinson et al., 1982). For high-frequency sounds the standing wave can resonate or anti-resonate, whereby it acts with the inward and backward signal, either by partially cancelling it, resulting in a lower signal level, or by fully cancelling the signal (Zebian et al., 2011). This could be a contributing factor to why some people have elevated SPL at certain frequencies within EHFs. It worth noting that the standing wave does not explain the overall trend of a rising minimum audible pressure (SPL) with frequency, but rather leads only to a dip at certain resonance frequencies.

[2] Reference equivalent threshold sound pressure levels (RETSPLs) are used when calibrating audiometric equipment to a hearing threshold level of zero at various frequencies.

2.3.2.2 ME attenuation hypothesis

The ME has a band-pass filter characteristic, as the efficiency of sound transmission by the ME is not equal across frequencies, so more energy can be transmitted for the mid frequencies than higher frequencies (see Section 2.1.1). The ME transfer characteristic has been assessed by previous studies using human cadaver temporal bones (Kurokwa and Goode, 1995; Aibara et al., 2000; Puria, 2003). The main ME forward pressure gain (i.e. the fluid pressure in the cochlea at the oval window relative to the ear-canal pressure) was 23–25 dB for frequencies below 1–1.2 kHz, reducing to 6–8.6 dB as frequency increased (Kurokwa and Goode, 1995; Aibara et al., 2000). Hence, it has been suggested that the ME transfer characteristics play a role in elevating HTLs in the EHF-range.

The transmission of sound energy through the ME works not only in a forward manner from ME to IE; it can also reverse-transmit sound energy sourced within the cochlea to the ear canal, as in OAEs. The forward pressure gain is influenced by EAC characteristics, and the reverse pressure gain is influenced by the cochlear function (Puria and Rosowski, 1996). The reverse energy can be detected by a sensitive microphone inserted in the ear canal; as in OAEs (Puria, 2003) the (round trip gain) forward and reversed pressure gain reached a peak at 1.3 kHz (-7 dB) decreased of approximately slope 11.7 dB per octave for higher frequencies. Therefore, the OAE is not just affected by the ME transmission of signal to the IE, it also takes account of the reversed energy from the IE transmitted through to the ME.

2.3.2.3 Cochlea sensitivity

Cochlear function may be attenuated at EHFs, as the TW might ‘run off’ at the basal end. Yasin and Plack (2005) have suggested that a full travelling wave peak may not be formed if the stimulus frequency is above the characteristic frequency at the most basal place on the BM. This run-off was probably only for frequencies > 17 kHz, based on PTCs (Yasin and Plack, 2005).

2.3.3 Suggested physiological differences in vulnerability at EHFs compared to CAFs.

As proposed by previous studies, EHF-hearing might be more susceptible to damage due to factors mentioned in Section 2.4, before changes in CAF-range. The cochlea may play an important role in the vulnerability of the basal end (tuned to EHFs), due to its characteristics and function. Basal end characteristics suggest that there may be a difference in blood supply between the two regions (Sha et al., 2001).

Animal studies reported the susceptibility of OHCs in the basal end of the cochlea, as these are affected by noxious agents (noise exposure and ototoxic medication) before apical region OHCs.

Noxious agents generate the overproduction of reactive oxygen species (ROS), which can damage the hair cells (Poirrier et al., 2010). Sha et al. (2001) suggested that from the histopathological findings of animal studies, the basal end of the cochlea has a lower glutathione (cellular antioxidant) level than the apical end, which can provide primary defence against free radicals. Lower concentrations of glutathione in the basal region lead to more production of ROS in this region, therefore more OHC damage can be observed in the basal region. This might be the reason behind changes in EHF-hearing (tuned in the basal end) being perceptible before those observed in the CAF-PTA, as reported in previous studies of human hearing. In research on human hearing, it is difficult to determine the actual mechanism behind the loss of hair cells, as we rely on psychoacoustic responses (indirect non-invasive measurements), as opposed to animal studies, which can use direct histological techniques.

2.4 Factors that can affect human hearing: causes of high frequency hearing loss

There are several factors that can negatively affect hearing, either independently or in combination with noise exposure. Factors can be endogenous, such as aging or hereditary loss, or exogenous, caused by, for example, drugs, noise exposure or infection (Duan et al., 2002). Susceptibility to these causes of HL varies between individuals (Carter et al., 2014; Royster, 2017), and their occurrence may be influenced by several factors, such as gender, inheritance, and lifestyle (e.g. whether someone is a smoker/non-smoker). Age-related HL, also known as presbycusis, is the most common form of hearing impairment in adults (Rabinowitz, 2000). Among the variety of environmental factors that can impact hearing, such as noise exposure, lifestyle, medication, and cigarette smoking (Kim et al., 2009; Mohammadi et al., 2009; Ohgami et al., 2011), noise exposure is the second most frequent cause of acquired HL in adults (Rabinowitz, 2000; Ahmed et al., 2001; Mehrparvar et al., 2014; Macca et al., 2015). HL due to aging, noise exposure and ototoxicity are known to affect high frequency sound perception. It has been suggested by Ahmed et al. (2001) and Mehrparvar et al. (2011) that this region of the cochlea is the first to show perceptible changes in hearing. However, this conclusion was based on cross-sectional observational data comparing HTL in a noise-exposed group with a non-exposed control group. The results may be affected by confounding variables, such as systematic differences in lifestyle between the two groups that are difficult to control. This is further discussed in Section 2.4.4.

Research shows that certain drugs, such as aminoglycosides, affect the high-frequency region. For example, one study reported that changes in auditory function due to ototoxicity were detected in EHF-HTLs before any obvious elevation was observed in CAF-HTL (Knight et al., 2007). Chauhan et al. (2011) investigated the effectiveness of EHF-HTL in detecting hearing loss due to ototoxic drug use. These findings indicate that measuring EHF-HTL is effective in detecting the early signs of ototoxicity. The most common causes of SNHL in adults, aging, is explained in detail in the following section.

2.4.1 Age-related hearing loss

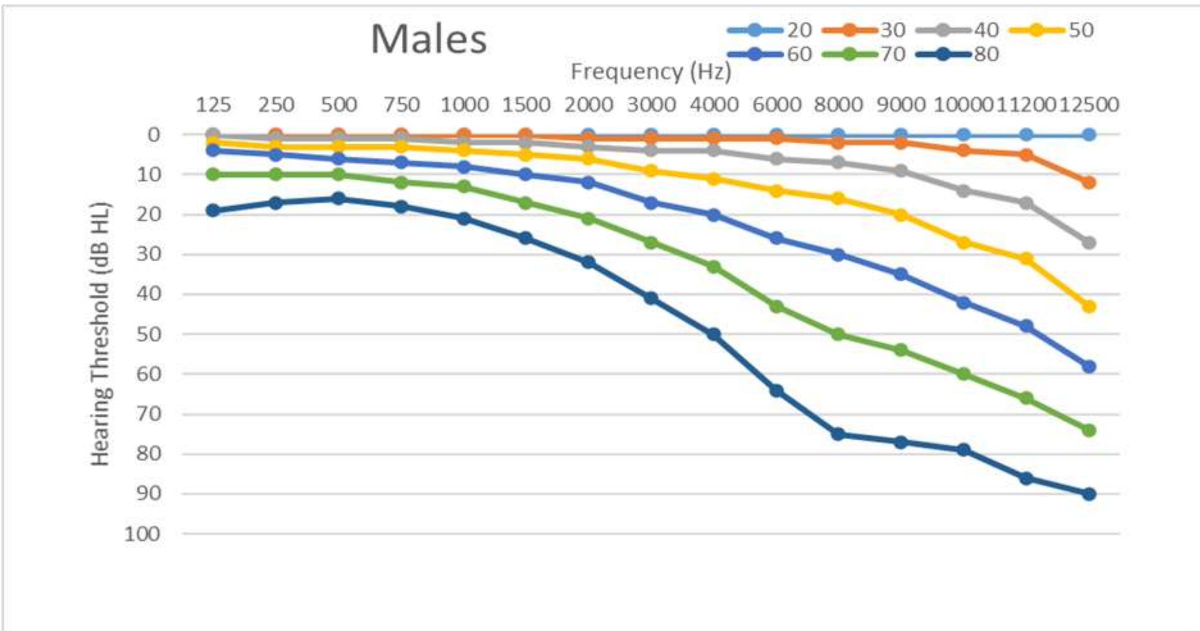
Over the age of 18 years, hearing sensitivity starts to decrease for some frequencies, especially EHFs, and by the age of 65 years and over, the chance of developing some degree of age-related SNHL increases (ASHA, 2016). This type of HL is typically bilateral and progressive, often recorded in the audiogram as high frequency sloping SNHL. With aging, sensitivity to sounds attenuates and extremely high-frequency loss begins (Lopponen et al., 1991; Ahmed et al., 2001; Somma et al., 2008). Over time the HL progresses to extend to adjacent low-frequencies. However, the degree of loss differs considerably between subjects, although it is likely to be greater in men than in women (Wiley et al., 2008). Age related HL is thought to be influenced by other factors such as noise exposure, genetics, and smoking and medical disorders (Gates et al., 1990; Huang and Tang, 2010). The literature has suggested that the combination of aging and noise exposure can make EHF-hearing more susceptible to damage, which can result in a decrease in hearing acuity that is apparent in the EHF-HTL first (Ahmed et al., 2001). To date there is no known way to resolve age-related hearing changes or a way to slow down the progression of its occurrence.

The effects of age on hearing were characterised by the International Organization for Standardization[3] (ISO)7029:2017, which describes the distribution of the expected hearing threshold in a population aged from 18 to 80 years without noise exposure that is expected to cause hearing damage. The distribution provides audiometric values for the standard frequencies and for frequencies between 9 and 12.5 kHz. It was shown that the values gradually increase with age for all frequencies, and this accelerates for older individuals, with the loss being greater in higher frequencies, and with hearing deteriorating more among males than females (ISO, 2017) (Figure 2.1).

Other authors have looked at the effect of aging on EHF-hearing (Lee et al., 2012; Rodríguez Valiente et al., 2014). Similar findings were reported by Rodríguez Valiente et al. (2014), who noted increases in HTL with increased frequencies and age, and lower (better) HTL in females than

[3] ISO is an international nongovernmental organization founded in 1946, aiming to brings together experts to share knowledge and to form consensus-based and commercial standards that support innovation and provide solutions to global challenges.

males. Lee et al. (2012) measured HTL up to 20 kHz and reported that the rate of increase in HTL with age appeared to be most rapid at around 16 kHz, with an increase of well over 1 dB/year from a baseline age of 10–20 years (although these results were from cross-sectional studies and hence potentially affected by confounding variables). There were no findings relating to gender difference in this, which may be related to the different calibration methods used in this study to ensure that the stimuli were individually compensated based on the depth of insertion of the probe into the subject's ear-canal during the test session. This attempts to compensate for the effect of the ear-canal length, which might be one reason why HTL in females is better as females have a smaller ear-canal.



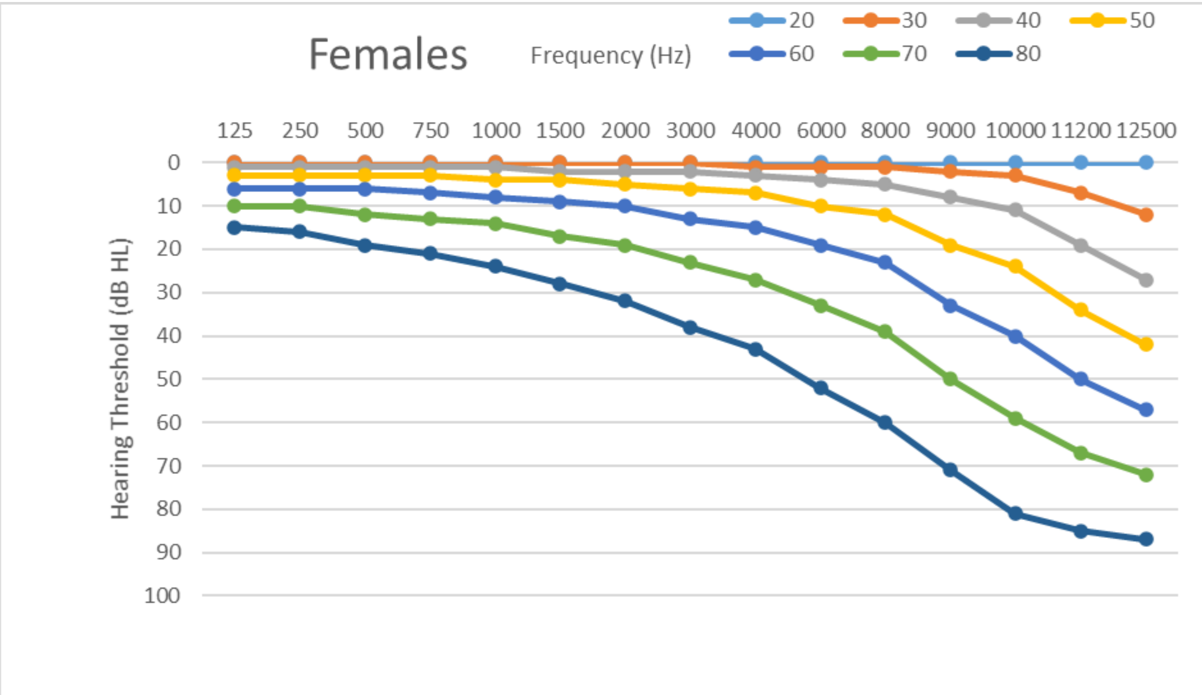


Figure 2.1: Effect of age on hearing, as characterised by ISO7029:2017 for males and for females. The x-axis plots the frequencies, and the y-axis the hearing thresholds (dB HL). The graphs illustrate the median of hearing thresholds at a given frequency for a particular age groups (18–80 years old in increments of 10 years).

2.4.2 Impact of diabetes on hearing

Several studies have investigated the impact of type II diabetes on hearing sensitivity, but results were controversial, as while some studies found an association between diabetes and hearing loss (Kurien et al., 1989; Forogh et al., 2013; Das et al., 2018), others disagreed and reported no relationship between them (Harner, 1981; Hodgson et al., 1987). This inconsistency in the results may be due to variations in the research methodologies applied. A meta-analysis by Horikawa et al. (2013) showed an association between diabetes (types I and II) and HL. Another meta-analysis has indicated that type II diabetic patients experience more HL than non-diabetic (Akinpelu et al., 2014).

CAF-PTA has been used by previous studies to ascertain the associations between diabetes and hearing loss. In a between-group comparison performed for both a control group and a diabetic type II-group, Forogh et al. (2013) found that HTLs were significantly higher in diabetic subjects, although the HTLs were within normal limits for both groups. Recently, a similar study by Das et al. (2018) showed that the HTLs of a group with higher glucose levels were higher than those of a control group for all frequencies. This study included an additional measurement of HTL, as EHFs (12 kHz) were compared between groups. The findings indicated that HTLs of a diabetic group were higher at EHFs than at CAFs. The longer the subjects had diabetes, the more the EHFs were affected (12 kHz), as well as the higher CAFs (8 kHz) but not the lower ones (1 and 4 kHz). Findings also showed that subjects who had experienced diabetes for longer than 10 years showed significantly higher HTL at 8 and 12 kHz compared to participants who had experienced diabetes for less than 10 years. The results also indicated that the duration of diabetes did not affect CAF-HTLs (other than at 8 kHz) for the diabetic group.

This research by Das et al. (2018) indicates that EHF regions are affected more in subjects with diabetes, and could mean that the assessment of EHF-HTLs can provide insight into early damage to hearing due to diabetes. The sensitivity of EHF measurements to hearing changes could be because this region is affected in diabetics earlier than the lower-frequencies, or it might be that there are other factors affect the basal region before any obvious changes can be observed in the CAFs, such as noise exposure and variation in lifestyle. In Das et al. (2018), information about noise history was not collected from participants and no distinction was made between diabetes types I and II.

2.4.3 Smoking as a risk factor in HL

Smoking is a factor known to be detrimental to health, and is associated with conditions such as stroke, high blood pressure, and lung cancer. Despite this (Prabhu et al., 2017), smoking is widespread among young adults. The effect of smoking tobacco on hearing loss is controversial. Chang et al. (2016) observed that smoking and passive smoking are both associated with HL. Their study found that smokers and passive smokers had more elevated (poorer) HTL among all age groups, and after the age of 40, passive smokers showed elevated HTL when compared to the non-smokers' age-matched group. This elevation in HTL could be the result of confounding variables e.g. lifestyle differences that are associated with smoking status and/or age-related HL. It may be that older subjects were exposed to smoking for a continuous longer duration, and that longer exposure would therefore have impacted the cochlea, resulting in changes in threshold that would only become obvious at an older age.

The association between smoking and hearing status was also indicated by Katbamna et al. (2007), who studied 24 young adults (12 smokers and 12 non-smokers). Subject inclusion was based on a self-reported history of smoking of 5–8 years. CAF-PTA was normal within both groups and EHFs showed age appropriate HTL across all subjects. However, the mean HTL for the smokers was statistically poorer than for the non-smokers, while results observed for DPOAEs showed poorer emissions for smokers compared to non-smokers. Likewise, Rogha et al. (2015) revealed that smoking is associated with hearing loss, as the HTL for the smokers group was higher than for the non-smokers at EHFs, and OAE amplitudes were lower than the non-smokers group. Hence, the available research could indicate that the effects of early signs of smoking on hearing in young adults can be detected by DPOAE measurements, therefore, DPOAEs may be considered a sensitive tool for detecting changes in hearing in the early stages

It is possible that smoking could also be a risk factor for NIHL, as some authors have reported that smokers have an increased risk of NIHL (Barone et al., 1987). The impact of high-level sound exposure and smoking habits on hearing threshold level was investigated by Ohgami et al. (2011) and Mehrparvar et al. (2015). Ohgami et al. (2011) detected differences in the average hearing of EHFs between the control (non-smokers) and the experiment group (smokers); both groups were exposed to similar noise; HTLs at 12 kHz were significantly higher for the smoking group. On the other hand, no differences were noticed in the hearing level for the CAF between the two groups (smokers and non-smokers). The authors suggested the inclusion of a 12 kHz hearing threshold measurement in the assessment of general health to detect hearing loss correlated with smoking. It worth noticing that confounding variables may weaken the validity of all these studies.

2.4.4 NIHL at EHF

2.4.4.1 Indications of NIHL using PTA

The consequence of over-exposure to noise can be NIPTS. It is characterised by bilateral SNHL, starting at high frequencies and then progressing to the mid- and low frequencies (Ahmed et al., 2001) but with a notch between 3-6 kHz, as already mentioned in Section 2.2.1. It has been suggested that damage to the cochlea due to noise exposure is slow in onset except for in cases of acute trauma, and it may take years to appear (Axelsson and Prasher, 2000). It is worth mentioning that there is variability between subjects' susceptibility to noise. The exact reason behind this variation is not fully known, as other factors can affect the development and the progression of NIHL, e.g. environmental and genetic factors. Therefore, it is essential to keep in mind that changes in hearing in noise-exposed groups could be due to a combination of other factors that coexist with the noise factor, as mentioned above, such as diabetes, smoking, and hypertension.

However, the findings of previous studies suggest that EHF might be a more reliable indicator than the CAF-HTL (the notch), making it the early signs of noise changes in hearing. The most effective way of identifying early-stage NIHL, in terms of CAF and EHF-HTL, still remains debatable. For CAF-HTL, the notch might occur when there is absence of any history of noise exposure (Nondahl et al., 2009).

With the recent interest in investigating the EHF-PTA, studies have suggested that EHFs might show elevation in HTLs more than the CAF notch (Ahmed et al., 2001; Mehrparvar et al., 2011; Wang et al., 2000), and therefore they might show signs of NIHL earlier than the notch. The issue of which frequency region is most vulnerable is a complicated one (i.e. notch in CAF region vs. EHF region). Although some studies have suggested that noise exposure is correlated with EHF-HTL more than CAF-HTL (Ahmed et al., 2001; Mehrparvar et al., 2011; Liberman et al., 2016), there is a lack of consensus, as others have suggested little relation (Wei et al., 2017). CAF-TEOAEs of < 6 kHz and CAF-DPOAEs of < 8 kHz have also been used to assess noise exposure impact and show lower amplitudes in noise-exposed individuals (LePage and Murray, 1998; Montoya et al., 2008) as discussed in Section 2.5.

As well as the question of CAF-HTL vs EHF-HFL, there could be an argument for the possible importance of both CAF- and EHF-HTL (i.e. together they might improve diagnosis or management). Wei et al., (2017) reported an association between EHF-HTL and audiometric notch at CAF-HTL. This could indicate the usefulness of combining both measurements to better diagnose NIHL, and therefore improve management.

Studies have suggested that EHF-HTLs are more affected by noise exposure than the CAF-HTLs. Ahmed et al. (2001) suggested that when exposed to noise, the EHF region of the cochlea is more vulnerable to damage than the CAF-range, as the EHF-hearing is the first to show perceptible changes. Results were gathered from a cross-sectional study on the effects of age and noise exosure, although confounding variables might potentially have skewed the results. Similar findings of greater elevation in EHF-HTL were detected in individuals with a history of exposure to noise, compared to non-exposed individuals at 12 kHz (difference of about 7–13 dB HL) and 14 kHz (difference of about 11–15 dB HL) (Mehrparvar et al., 2011; Sulaiman et al., 2014, Macca et al., 2015).

Measuring occupational noise exposure using EHF-HTL has been the focus of several studies. EHF-HTLs were observed to be higher for noise-exposed groups (about 15–29 dB HL difference for 14 and 16 kHz) after controlling for age (Mehrparvar et al. 2011; Macca et al. 2015). The difference between HTLs for the two groups was reported to increase with increasing frequencies, although this obviously depends on the intensity and duration of noise exposure, since the longer the duration of the exposure, the more elevated the HTL. In addition, Ma et al. (2018) reported that EHF-HTLs for an occupational noise-exposed group of 20–39 years of age were about 3 dB and 8 dB HL (for CAF and EHF-HTL) higher than the age-matched non-noise exposed group. In contrast, Wang et al. (2008) reported that HTL was affected by noise exposure in the exposed group at both CAF and EHF-HTL, with the maximum difference between groups being 4 kHz (19 dB). This may be due to the differences between the study populations or study methodologies, such as the type and degree of noise exposure, the age of the samples and other lifestyle factors that may have interacted with the NIHL.

Previous studies have been conducted to investigate the impact of PLD use on hearing status (Sulaiman et al., 2014; Sulaiman et al., 2015; Kumar and Deepashree, 2016). HTL for frequent PLD users showed higher EHF-HTL (of about 3–12 dB HL) when compared to age-matched non-users, though the difference between groups increased with increasing frequency (Sulaiman et al., 2014; Kumar and Deepashree, 2016). Accordingly, we can conclude that recreational noise exposure may also affect hearing in similar ways to that of occupational noise exposure. Sulaiman et al. (2014) also examined the effect of PLD exposure on hearing, showing that compared to a control group, the EHF-HTLs were significantly higher for the PLD users.

It is thought that hearing worsens in users who listen to devices at high volume than in those who use low volume. In addition, as would be expected, hearing levels were also affected by the duration of PLD use; participants who had used PLDs for longer than five years had significantly higher thresholds than those who had used them for less than five years (Kumar and Deepashree, 2016).

A recent longitudinal study assessed the hearing sensitivity of CAF and EHF-HTLs in shipyard workers exposed to occupational noise (Jiang et al., 2021). This study included both cross-sectional and longitudinal data. For the cross-sectional data, a linear regression analysis of HTLs was performed on cumulative noise-exposure at individual frequencies from 3 to 12.5 kHz, for groups stratified by age. The authors found that HTL was most sensitive to cumulative noise exposure at 12.5 kHz, which was statistically significantly different from the sensitivity at 4 kHz. In the 4-year long longitudinal study of noise-exposed workers under the age of 40 years, the study found a greater rate of change of HTL over the 4 years at 12.5 kHz than at 4 kHz at 2.70 dB/year and 1.25 dB/year, but this included the effects of both NIHL and ARHL. This was separate from the findings of the cross-sectional study.

2.4.4.2 **Hidden hearing loss**

Recent results from animal studies have suggested that noise exposure leads to TTS, and that even when the HTL and DPOAEs have returned to their normal values, there may have been permanent harm to the cochlea, resulting in a phenomenon that has been termed “hidden hearing loss” because there is damage to the auditory system that does not show up in the audiogram (i.e. as NIPTS). The term “synaptopathy” has been applied to the type of damage reported by Liberman’s group in their animal studies. Kujawa and Liberman (2009) investigated TTS in mice, performing a histological assessment on animals’ recovery after TTS (shift up to 40 dB). Recovery was assessed based on DPOAEs and auditory brain stem response. It was revealed that almost 50% of the synapses between the IHCs and the afferent auditory nerve fibres were permanently lost, as the damage was selective to the low spontaneous rate auditory nerve fibres. This finding contradicts the assumption that TTS is not an indicator of permanent damage to the auditory structures and raises the question whether this damage may also occur in humans. It was hypothesised that in humans this damage may cause difficulty in understanding speech in complex situations, i.e. noisy backgrounds. Unfortunately, investigating speech perception cannot be applied to animals, so investigating this hypothesis has been tested recently in humans (Bramhall et al., 2015; Liberman et al., 2016; Bramhall et al., 2017).

Several studies have used EHF from 8 kHz to 16 kHz auditory evoked potentials and speech tests in noise to detect the presence of hidden hearing loss (HHL). Liberman et al. (2016) performed a cross-sectional study to investigate HHL in young adults who were divided into a high-noise exposure and a low-noise exposure group based on their self-reported exposure to noise. The hearing of both the high- and low-noise exposure groups was measured using PTA, EHF-PTA, and word recognition tests in both quiet and noisy settings. Cochlear health was assessed by OAEs and electrocochleography (ECochG). The results of this study revealed that standard PTA indicated normal measurements for both groups, while EHF was elevated in the high-noise exposure group. Additionally, the high-noise exposure group showed similar scores to the low-noise exposure group in word recognition tests in quiet conditions, but their performance was poorer in the noisy situation. Furthermore, ECochG showed a higher summating potential/action potential ratio in the high-noise exposure group than in the low-noise exposure group. The study concluded that ECochG, EHF-PTA, and speech tests in noise may be useful tools for detecting the presence of HHL. This finding was confirmed by studies by Bramhall et al. (2015, 2017), which took a similar approach to the previous study.

Prendergast et al. (2017) included a larger sample size (n=126), but their findings were different to Liberman's, in that individuals with normal audiograms at CAF-range did not show any evidence of reduction in wave I amplitude with higher noise exposure. It has been suggested that the results from animal experiments regarding noise exposure do not directly correspond to results for human subjects (Prendergast et al., 2017). For example, 100 dB SPL for 120 minutes may be enough to produce a synaptopathy in mice, while in a human this amount of exposure to noise may not result in any damage to hearing. The debate continues as to the existence of HHL in humans and as to the best procedures for detecting and assessing HHL.

2.4.4.3 **Evoked otoacoustic emissions**

As mentioned in Section 2.3, OAEs are low intensity sounds that can be recorded by a probe in the external ear canal. Both TEOAEs or DPOAEs are elicited in response to an external stimulus (Katz, 2015). TEOAEs are elicited as a response to a brief acoustic stimulus, e.g. a click or tone burst. Subsequent to the onset of the stimulus, the response occurs after a brief time delay. When the click, which is a wideband stimulus, is presented as the eliciting stimulus, a wide area of the cochlea will be stimulated, and therefore the response will be presented with a wide range of frequencies from different parts of the cochlea. Kemp (1978) stated in his initial report using TEOAEs that the responses of different frequency components appear at different latencies, as the high frequency component of the response occurs at an early time window, while low frequency components appear at later latencies.

DPOAEs are produced in response to two pure tone stimuli which are close in frequency and are presented to the ear simultaneously; these are known as "primary tones" f1 and f2. They vary in frequency with f2 > f1, with corresponding levels L1 and L2. In response to these frequencies the cochlea will produce energy at other discrete frequencies, which are arithmetically related to the primary tone frequency ratio (i.e. f2-f1, 2f1-f2, 3f1-2f2, 2f2-f1). In human ears the most prominent

DPOAEs appear at the frequencies 2f1-f2. The DPOAEs arise from the nonlinear mechanism of the cochlea and are more frequency specific and less sensitive to HL than the TEOAEs.

2.5 Mechanisms of cochlear damage in the EHF hearing

Noise exposure might contribute to the effect on the basal turn of the cochlea, leading to loss at the EHF hearing. The theories are not just limited to damage in the OHCs but might also concern the neural section of the cochlea. OHC damage is long thought to be the main source of NIPTS due to noise exposure (Franklin et al., 1991; Hamernik & Qiu, 2000). Recently, it has been suggested that some of the early changes in noise exposure damage take place at the level of the synapse (Kujawa and Liberman, 2009) and can be referred to as IHC synaptopathy. Another perception was that noise exposure might impact the OHC efferent system (medial olivocochlear neuron, MOC) (Lalaki et al., 2011) due to the reduction in the auditory nerve afferent neural activity. This might lead to reduction of neural signals via the MOC bundle, which may be due to the direct effect on the OHC efferent synapses that reduce the efferent feedback control of OHCs. Table 2.2 shows the assumption of the proposed theories for damage in the auditory system due to noise exposure.

Table 2.2: Theories of original damage in cochlear due to noise exposure

Theoretical aspect	Damage origin
Synaptic structures	IHCs synapses(1)
Cochlear neurons	OHCs MOC efferent nerves(2)
Hair cells	Cochlear OHCs

[1]. Proposed by Kujawa and Liberman (2009).
[2]. Proposed by Lalaki et al. (2011).

The first theory proposed assumed that hearing changes due to noise are a result of OHCs damages (Hamernik & Qiu, 2000). Similar to OHCs damage (i.e. lead to reduced cochlear amplification), the hearing sensitivity to quiet sound is affected. Recently, there are other proposed theories (Table 2.2) that suggest other mechanisms of noise exposure damage, which might be observed without significant permanent OHC damage. The impact on IHC synapses does not lead to NIPTS (“hidden” hearing loss), but only leads to suprathreshold impairments because it preferentially affects the low spontaneous-rate neurons. Liberman et al. (2016) reported that damage in IHCs might contribute to speech-in-noise difficulty, reduction in wave I amplitude, and EHF-HTL shift in the absence of any CAF-HTL shift. However, no statistically significant shift in EHF-DPOAEs was observed. There are two possibilities for the EHF-HTL shift; one is that the EHF-HTL shift is due to IHC-S e.g. shift is associated with the high-spontaneous rate neurons effect. Another possibility is that in the EHF region, the OHCs might be damaged, so the EHF-NIPTS is due to the greater vulnerability of OHCs than at CAFs. In this case, the lack of EHF DPOAE shift is due to the inherent variability in the EHF region (i.e. it was a false-negative type II error). The impact is greatest at EHF; it is not fully understood why EHF are most vulnerable. Although, it has been suggested that this might be due to differences between basal and apical end characteristics such as blood supply (Bachor et al., 2001), but it is unclear which part of the cochlear that affect whether it is OHCs or IHCs. The suggestion of why the speech in noise was affected might be that the loss is selective to low spontaneous rate that are thought to encode information in background noise (Young & Barta, 1986). This proposed theory is suggested that the synapsis is the first to be affected before any damage is observed in OHCs of the cochlear (Kujawa and Liberman, 2009).

The second theory is related to damage of the cochlear AN, which includes the MOC efferent nerves that project to the OHCs for regulation (Zhao et al., 2022). The cochlear efferent system plays a significant role in hearing, such as the regulation of hearing sensitivity and improves speech discrimination in background noise (Guinan, 2006). Therefore, damage to the OHCs efferent might lead to difficulty in understanding speech in difficult situations and altered amplitude of TEOAEs (Lalaki et al., 2011). However, the exact mechanisms for how the efferent system controls hearing sensitivity and improves discrimination still remains largely unclear.

Finally, the concluding theory was due to dysfunction or loss of OHCs, which leads to a loss of sensitivity (worsens HTL), a reduction in frequency selectivity, and reduced TEOAEs amplitude. As proposed by previous studies, EHF hearing might be more susceptible to damage due to factors mentioned in Section 2.4, before changes in CAF-range. This might be due to that basal end characteristics suggest that there may be a difference in blood supply between the two regions (Bachor et al., 2001).

2.5.1 Audiogram fine structure

Damage in OHCs is likely to affect OAE amplitude, HTL elevation, AFS ripple depth, and AFS spectral periodicity (further explained in Chapter 5). On the other hand, IHCs may have no effect on any of these. One reason explained, HHL leads to suprathreshold impairments because it preferentially affects the low spontaneous-rate neurons. Another reason is the active amplification of OHCs (the main requirement for these phenomena). This may only have an effect on HTL elevation (via IHCs of high-spontaneous rate neurons, if this occurs), but would not greatly affect the other phenomena that arise from OHC amplification. Furthermore, OHCs might affect amplification via the MOC route, but this is likely to be small, and it is not clear which direction the effect would be. In normal hearing, MOC excitation reduces activity, so it might be predicted that OHCs would increase rather than reduce OHC activity (Lalaki et al., 2011).

The rationale for study 2 is then to establish whether there are significant differences between a number of phenomena related to OHC activity in the EHF region compared to those found in the CAF region. These phenomena are not thought to be greatly affected by IHCs. If no clear differences exist, it might indicate that some of the OHC phenomena at CAF also show up at EHFs. If they do not, then these differences will require further explanations (that will be further explained in Chapter 5).

2.6 Relationship between noise-exposure and CAF-OAEs

Since OHCs are assessed by the OAEs, the use of OAEs in detecting NIHL has been investigated. Several studies performed on humans have suggested that OAEs may provide an indication of early signs of noise damage in the cochlea before any sign of HL in the CAF-audiogram (Desai et al., 1999; Lapsley Miller et al., 2004; Seixas et al., 2005; Konopka et al., 2005).

Desai et al. (1999) reported the presence of TEOAES at CAF-range among a non-exposed group, but emissions were absent in almost 60% of their noise-exposed group, despite normal audiograms for both groups. Konopka et al. (2005) found a reduction in the amplitude of CAF-TEOAEs and elevation in EHF-HTL after one year’s exposure to impulse noise, while no statistically significant changes were indicated by CAF-PTA. Thus, it is suggested that OAEs may detect changes in hearing status before any obvious difference in CAF-PTA.

The CAF-TEOAE method is quick and easily applicable, and it shows good test-retest reliability (Harris and Probst, 1991). The possibility of using TEOAEs as a screening and monitoring tool for cochlear changes in a noise-exposed population was investigated by Hotz et al. (1993), who recorded CAF-TEOAEs during seventeen weeks of military exposure (firearm use). Subjects with normal CAF-PTA were assessed using TEOAEs before and after the military training course, during which some participants were required to wear hearing protection during the exercises. It was reported that after the course, emission amplitude had decreased in the frequency range from 2 kHz to 4 kHz, and the reduction was greater in the more exposed group. Due to equipment limitations, which meant that frequencies of more than 4 kHz were not measured, it was suggested that the administration of DPOAEs would be useful to allow reliable tests at higher frequencies. Hence, these authors suggested that TEOAEs may be used as a screening tool, since this technique is less time consuming than CAF-PTA and provides reliable measurements.

In addition, a study performed by Biassoni et al. (2014) considered the long-term effects of recreational noise exposure on adolescents. The hearing of 59 males was assessed at age 14–15 years using CAF-PTA, EHF PTA (8–16 kHz), and TEOAEs. The participants were then retested at age 17–18 years, and a questionnaire covering information regarding noise-exposure was completed by the participants during the test and re-test evaluations. An increasing tendency to engage in recreational activities over time was reported by the subjects, indicating an increase in young adults' tendency to participate in unsafe sound level activities as they get older. Therefore, it was not surprising that the results showed a significant increase in hearing threshold level at all frequency ranges, and a significant reduction in the amplitude of TEOAEs in the normal hearing group, with greater difference noted between the baseline HTL and follow-up HTL in the high noise exposure group.

All of these studies (Biassoni et al., 2014; Konopka et al., 2005; Hotz et al., 1993) reported similar findings, i.e. that the noise-exposure groups had lower CAF-TEOAEs than the non-noise exposure groups. They also reported a reduction in TEOAE amplitude, which correlated with noise exposure and suggested that low levels of TEOAEs with normal CAF-HTL could indicate subclinical damage in the cochlea. On the other hand, Williams et al. (2015) disagree with these findings. They examined the relationship between self-reported cumulative life-time noise exposure and CAF-PTA, TEOAEs, and DPOAEs, and reported no correlation between calculated cumulative noise exposure and PTA or OAEs. This inconsistency in the findings may be because noise-exposure is difficult to measure accurately. In the above study, it was judged subjectively via self-reported responses, which may have led to overestimating the accumulation of noise exposure. Another explanation could be that the level of noise exposure was different to that in the previous studies (i.e. higher noise level).

A longitudinal study by Seixas et al. (2005) reported that changes in CAF-DPOAEs correlated more strongly with noise exposure than changes in CAF-HTL over 4 years. In addition, Lapsley Miller et al. (2004) examined the effect of noise-exposure on CAF-TEOAEs, CAF-DPOAEs and CAF-PTA. The results revealed that the noise-group's HTL statistically significantly increased by 1.2 dB and the amplitude of their CAF-DPOAEs decreased by 1.3 dB for frequencies between 2 kHz and 4 kHz over 2 years, while no statistically significant changes were noticed in the non-exposed group. Additionally, both the groups showed a decrease in CAF-TEOAE amplitude between 2 kHz and 4 kHz of around 0.6 to 0.7 dB, with the noise-group recording a slightly greater reduction in the amplitudes. However, the researchers stated that this decrease in both groups may not necessarily be related to noise alone, but may also be related to the aging process, as TEOAEs at high-frequencies are more affected by both noise and aging than the lower frequencies.

These longitudinal studies suggested that changes in the CAF-OAE and CAF-HTL do not necessarily occur together for both groups. This might correlate with variations between subjects, as each subject might have a different exposure tolerance, vulnerability to NIHL, and lifestyle, in which case these variations can affect the actual group alignment. Thus, while studies suggest that TEOAEs are a promising tool for detecting hearing changes due to noise exposure, this technique may not yet be suitable for monitoring hearing in hearing conservation programmes, since it does not yet have good validity and reliability.

It has been speculated that absolute OAE amplitude might not be a good predictor of HTL for several reasons. One is that TEOAE and DPOAE inter-subject differences in ME transmission can reduce the correlation between OAEs and PTA (discussed in further detail in the following chapters). In the case of TEOAE it arises when there is both active amplification of the travelling wave and multiple reflections of the travelling wave between apical and basal sites, while HTLs are largely independent of the multiple reflections. For DPOAEs it arises from two sources, nonlinear distortion that results from traveling waves, and reflection sources.

There is currently a lack of knowledge of the use of high-frequency OAEs and further studies are needed in this research field.

2.7 Relationship between noise exposure and EHF-OAE

There is a relatively small body of research investigating the use of high-frequency OAEs (above 8 kHz for CAF-DPOAEs and 6 kHz for CAF-TEOAEs) as an indicator of cochlear changes, especially due to the effect of noise. It has been speculated by Goodman et al. (2009) that measurements of high frequency OAEs could be useful for detecting and monitoring high-frequency hearing loss (Goodman et al., 2009; Keefe et al., 2011). The physiological mechanisms behind EHF-DPOAEs are the same as those for CAF-DPOAEs (Dreisbach and Siegel, 2001). According to Dreisbach et al. (2006), who investigated the repeatability of EHF DPOAEs (up to 16kHz) in normal hearing young individuals, the measurements were repeatable and reliable with a decrease in the DPOAE response compared with lower frequency recordings. Liberman et al. (2016) investigated differences in EHF DPOAE amplitudes of up to 12 kHz between noise and non-noise exposed groups, but no significant differences were reported between groups with regard to the EHF DPOAE amplitude.

Since the EHF-range may be affected before the CAF, and DPOAEs have been indicated to be reliable and sensitive to cochlear damage; DPOAEs with high-frequency stimuli may be useful for hearing monitoring in subjects exposed to noise and ototoxic drugs. Thus, testing in this area would be beneficial to detect any defect that may start in that region.

2.8 Calibration of EHF-PTA and OAEs

Due to ear canal characteristics, calibration at high frequencies can be problematic for stimuli presented by an earphone in or near the entrance to the ear canal (affecting both PTA and OAEs), and for OAEs emitted from the tympanic membrane and measured with a probe near the entrance to the ear canal (affecting OAEs).

The complications of calibration result mainly from multiple reflections of sound waves travelling in the ear canal.

2.8.1 Stimulus calibration for PTA and OAE evoking stimulus

Both PTA and OAEs require stimulus calibration; the calibration accuracy varies between CAF and EHF ranges. For measurements at CAF (< 8 kHz), the standard clinical calibration method is to quantify the intensity of a stimulus by presenting the stimulus to an ear simulator and measuring the SPL at the reference microphone. Ear simulators are designed to have the same acoustical properties as the average adult ear, such that the SPL measured at their reference microphone is the same as the SPL that would have been measured at the tympanic membrane of an average ear (for the same voltage signal driving the earphone). The stimulus amplitude at the reference microphone measured in dB re 20 uPa can be converted to a hearing level in dB HL using known RETSPLs. Ear simulators currently in use are designed to match the average adult ear canal up to 10 kHz (IEC 60318-1:2009, IEC 60318-4:2010); above 10 kHz, it becomes more difficult to design ear simulators as the frequency response of the ear becomes more complex, and there is greater inter-subject variability, therefore it becomes unrepresentative of an average ear (IEC 60318-4; 2010; Rodrigues et al, 2014). Furthermore, the ear simulator will differ from individual ears to differing degrees, leading to individual differences in the spectrum of the stimulus at the ear drum. Due to standing waves, the stimulus level at the ear drum is increased by constructive interference at half-wave resonances, typically at about 8 and 16 kHz. Nevertheless, the ear simulator can still be used as a standard reference coupler which has allowed RETSPLs to be defined up to 16 kHz (ISO 389-5:2006) for certain transducers.

When calibrating stimulus in the EHF region there are several issues which arise because of the influence of standing wave components in the ear canal that arise from multiple reflections at both the tympanic membrane and at the entrance of the ear canal via the earphone. This shows more inter-subject variability as well as greater intra-subject variability due to changes in the insertion depth of the earphone (for insert phones or OAE probes), compared to stimuli at CAF-frequencies. The standing waves lead to an amplification of the SPL at the tympanic membrane (relative to the case where reflections at the ear canal entrance are suppressed) at integer multiples of the so-called “half-wave resonance frequency” of c/2L, where c is the speed of sound, and L is the effective length of the ear canal. The first half-wave frequency (c/2L) occurs at stimulus frequencies close to 7 kHz and the second (c/L) at 14 kHz in typical ear canals, but the exact values vary depending both on the individual ear and on the depth of insertion of the earphone.

Several methods have been suggested for reducing the effects of multiple reflections in the ear canal (reviewed in Souza et al. 2014) and for providing a calibration that is individualized for each test ear. The method that is currently favoured is to estimate the so-called “forward pressure level” (FPL) of the stimulus, which corresponds to the sum of all the sound waves in the ear canal that are directed inwards from the earphone towards the ear drum — i.e. the initial wave launched from the earphone, plus all the subsequent waves leaving the earphone to travel inwards that arise from multiple reflections within the ear canal (Souza et al., 2014; Charaziak and Shera, 2017). This method requires the stimulus to be delivered by an OAE probe that provides a measurement of the pressure at the entrance to the ear canal. It also requires additional calibration equipment to allow the earphone to be characterised by its so-called “Thevenin equivalent” source parameters, as well as a measurement in the individual’s ear that allows the tester to estimate the reflection coefficient of the individual’s ear drum and of the termination at the entrance of the ear-canal. This then allows the FPL to be estimated from the SPL at the entrance to the ear canal (Souza et al., 2014; Charaziak and Shera, 2017).

It should be noted that at the “quarter-wave null frequencies”, the raw SPL at the ear canal entrance (i.e. the SPL without correcting for multiple reflections) becomes a very poor predictor of the SPL at the eardrum, with typical discrepancies of over 20 dB SPL. The quarter-wave null frequencies are frequencies at odd-integer multiples of c/4L, which typically occur at around 3.5, 10.5 and 17.5 kHz (for typical ear canal lengths and probe insertion depths). For this reason, the use of the individually measured SPL at the ear-canal entrance using the OAE probe is not recommended; instead, it is better to use the SPL in the ear simulator, or better still to use the calculated FPL (if the equipment and measurement time allow).

It should be further noted that the presence of reflections in the ear-canal does not completely invalidate the use of the ear-simulator as a method of calibration. The RETSPLs that have been obtained up to 16 kHz (ISO 389-5:2006) will include the effects of the reflections that occurred in the ear canals of the test sample that was used to obtain the RETSPL. The main disadvantage of using the ear canal simulator rather than the FPL method is that there will be somewhat greater inter-subject variability (Souza et al. 2014), for hearing threshold level, and a greater sensitivity to the depth of insertion when using insert earphones.

As well as the issue of calibrating the stimulus level at EHFs, there is also the issue of calibrating EHF-OAE amplitudes, which has led to the definition of the emitted pressure level (EPL). Unlike the FPL that estimate the energy level at the TM, the EPL estimate the intensity level at the EAC.

2.8.2 Calibration method in the current study

In the current study, rather than use the FPL calibration method, it was decided to use the standard ear simulator method both for the stimulus used in PTA and that used in evoking OAEs. The standard clinical method of calibrating the measured OAE SPL was also used, rather than the EPL. While the FPL/EPL method would most likely reduce some of the unwanted inter-subject variability in the outcome measures associated with inter-subject variability in the ear canal dimensions, this method takes more measurement time per participant and requires more expensive equipment than the standard ear-simulator calibration techniques. Furthermore, in the current study, the outcome measures used for testing the research questions were based on averages over several frequencies, which tend to average out the effects of inter-subject differences in individual half-wave resonance frequencies.

Note that a considerable increase in inter-subject differences at the EHF-HTL compared to CAF-HTLs is observed, even after taking account of the effects of ear-canal acoustics using FPL or similar techniques, which indicates that most of the increased inter-subject variability in EHF-HTLs arises after the outer ear canal, i.e. in the ME, IE or more centrally (Lee et al., 2012).

Chapter 3 The relationship between high-frequency hearing and noise exposure (Study 1A: Cross-sectional data)

3.1 Introduction

NIHL is often assessed by CAF-PTA, with the diagnosis made according to the presence of a notch between 3 kHz and 6 kHz in the audiogram, and an associated history of noise exposure (Nelson, 2005). However, previous studies have suggested that noise exposure might affect the basal end (tuned to EHF sounds) of the cochlea, before the apical region (tuned to CAF and perhaps before the 4 kHz characteristic place) (Sha et al., 2001; Porto et al., 2004). Several reasons have been proposed as to why the basal region can be more vulnerable than the apical. One of these concerns cochlear lability, since basal end characteristics may lead to differences in blood supply between the two regions (Sha et al., 2001) (Section 2.3.3).

It is assumed that any sound exposure for Leq above 85 dBA might potentially be damaging to hearing (ISO 1999, 2013 and HSE, 2015). In the current study, it is assumed that if the subject is exposed to noise and is quantified with NESI of 10 units for 10 years, it is equivalent to exposure to 90 dBA working days for 10 years. Therefore, the originally designed criteria is that if the subject scored more than 10 for the NESI score, then they were classified in the exposed group. Unfortunately, due to the unsuccessful recruitment attempt from the music production and music department, the planned cut-off point was reduced according to the NESI score, which was calculated as the median of the sample included in the study.

In the current study, musicians were targeted due to the expectation that musicians and music technology students are likely to be exposed to higher than average levels of noise exposure.

Previous research into human hearing have suggested that HTLs in the EHF range are higher than those in the CAF range, and this is likely to be due to noise exposure (Ahmed et al., 2001; Mehrparvar et al., 2011). Liberman et al. (2016) have also reported elevation in EHF-HTLs for a noise-exposed group (most of the participants were music students) compared to the non-exposed group, whereas CAF-HTLs were similar for both groups. They also investigated differences in EHF-DPOAEs of up to 12 kHz in amplitude between both noise and non-noise exposed groups, but no statistically significant differences were reported between groups for CAF-and EHF-DPOAE amplitudes. These previous studies are cross-sectional in design, and thus there may be potential confounding variables affecting the findings. Such confounding variables could be, for example, that frequent music concert attendance may also correspond to higher alcohol consumption, less sleep, and a less healthy diet than infrequent concert attendance.

Some research has used EHF-DPOAEs to investigate the effect of ototoxic agents on hearing (Reavis et al., 2011; Dreisbach et al., 2018; Poling et al., 2019), while others have focused on noise exposure (Liberman et al., 2016; Narahari et al.2017; Dhrruvakumar et al., 2021). An experimental study by Narahari et al. (2017) gathered data from participants to obtain both baseline and follow-up DPOAE data, with the follow-up conducted two hours after PLD usage. They reported no significant reduction in CAF measurements, while EHF-DPOAE amplitudes showed a statistically significant reduction. Thus, the findings suggested that EHF-DPOAEs could be an effective tool for early detection of noise exposure hearing loss, but further investigation is needed in this field. Dhrruvakumar et al. (2021) reported lower EHF-DPOAE amplitudes in a noise-exposed group, and a statistically significant difference between the EHF-DPOAEs of the noise-exposed group and those of the non-noise exposed group.

The current study examines the DPOAEs, TEOAEs and HTLs up to 16 kHz in order to compare the differences in measurements between participants with heterogenous degrees of recreational noise exposure. The recreational noise exposure was quantified using the NESI questionnaire, and the methodology is explained more fully in Section 3.4.5 below.

One of the novel components of the current study is the use of the double-evoked paradigm to evoke TEOAEs, which allows EHF-TEOAEs to be measured. This is described in more detail in Section 3.4.3.2 and in Chapter 6.

This is a cross-sectional study where there is a risk of confounding variables such as smoking, alcohol consumption or diet that may be correlated with noise exposure. However, in the current sample study, there is not enough statistical power to control the confounding variables. A study with an extremely large sample size is needed to adequately control for the variables.

3.2 Research Aims and Questions

Aims

Aim 1. To assess the sensitivity of CAF and EHF hearing measurements to the effects of noise exposure in young adults, as assessed by the NESI questionnaire. The measurements used are HTLs and the amplitudes and SNRs of DPOAEs and TEOAEs.

Research Questions

- RQ 1a. do hearing measurements show greater sensitivity to NESI score at EHFs than at CAFs when the NESI score is treated as a continuous variable?
- RQ 1b. do hearing measurements show greater dependence on NESI score at EHFs than at CAFs when the NESI score is used to define two noise exposure groups (low- NESI groups and high- NESI groups).

The reason for using two different analysis to assess the effect of NESI score was to cross-check the validity of the results given that the distribution of NESI scores shows that the high influence of a small number of participants (who were tested for RQ1a) swayed the results.

Aim 2 and RQ 2. To assess which parameters of EHF-TEOAEs and EHF-DPOAEs lead to the highest signal amplitudes and highest SNRs and therefore may be optimal for clinical applications.

- RQ 2a: this refers to RQ 2 for EHF-DPOAEs, which were measured using two paradigms (one a low-stimulus and the other a high-stimulus level paradigm), termed here the “70/70” and “65/55” paradigms. These are explained in detail in Section 3.4.4.
- RQ 2b: this refers to RQ 2 for EHF-TEOAEs that were measured using two stimulus paradigms termed here the high-pass filter (“HPF”) and toneburst (“TB”) paradigms, these are explained in detail in Section 3.4.3.1.

Aim 3. To assess how well OAE measures predict EHF-HTLs. For example, when cochlear damage (e.g. due to age or noise) is indicated by EHF-HTL, is it possible to ascertain which OAEs can predict this damage? That is, which OAEs correlate most strongly with EHF-HTL?

- RQ 3. how strongly do different EHF measurements correlate with each other, and with measurements in the CAF range? Specifically, what is the bivariate correlation matrix between HTLs, DPOAEs and TEOAEs, with these measurements averaged separately over the CAF and EHF ranges?

3.3 Methods

The study was conducted over sixteen months and comprised both cross-sectional and longitudinal parts. It is hypothesised that noise and/or age may lead to hearing damage in the EHF range before damage in the CAF range. This chapter concerns the cross-sectional part of the study, looking at and analysing the baseline data. This chapter assesses the sensitivity of EHF and CAF hearing measurements to the noise-exposure metric by evaluating the data using within-subject and between group designs.

3.3.1 Sample size calculation

The aim was to recruit fifty participants to assess the relationship between NESI score and hearing measurements. The sample size calculation was based on the need to detect differences in the effects of noise exposure on EHF-HTLs compared to CAF-HTLs. Liberman et al. (2016) reported a difference between EHF-HTL and CAF-HTL of almost 9 dB in a group of high- risk group, compared to no significant difference between EHF and CAF in a control group. The standard deviation (SD) of HTL in the population was estimated from the interquartile ranges (IQR) in the following ISO standards, which describe the distribution of HTLs for CAF (ISO 7029; 2017) and for EHF (ISO 28961, 2012), using the relationship that SD = IQR/1.34 for an approximately normal distribution. Assuming the SDs are the same in both high- and low- NESI groups, the SD of the difference in HTL between the high-exposure and low-exposure group is the √2 times the HTL in each group. Hence:

SD for (HTL High-NESI of CAF - HTL Low-NESI of CAF) is 1.41x5.8[4] = 7.76 dB

SD for (HTL High-NESI of EHF - HTL Low-NESI of EHF) is 1.41x10.5 [5] = 14.9 dB

This gives an effect size of 0.75 and a required sample size of 58 (for 80% power, 5% alpha, 2-tailed test). This assessment has the non-conservative assumption that the SD is the same in both the high- NESI group and low- NESI group (it is likely to be higher in the high- NESI group) but also uses the highly conservative assumption that there is no correlation between CAF-HTLs and EHF-HTLs, despite these measurements being repeated within each participant. This also assumes that

[4] 5.8 dB is the standard deviation (SD) and is estimated from the interquartile ranges in the ISO 7029, averaged over 3 frequencies (4, 6, and 8 kHz).
[5] 10.5 dB is the SD estimated from the interquartile ranges in ISO 28961 averaged over 6 frequencies (10, 11.2, 12, 12.5, 14, and 16 kHz).

the sample has experienced similar noise exposure to that in the Liberman study, though the level of noise exposure was not quantified in Liberman study.

3.3.2 Participants

The participants were young adults (18–34 years) with normal hearing in the CAF range (as defined in section 3.3.2.1). Only one ear was tested per subject, recruits where from three groups: University of Southampton (UoS) music department, Solent University music production department and UoS non-music departments. All subjects were recruited by poster, word of mouth or via email to selected known acquaintances (see Table 3.2 for details of participant recruitment). There are several reasons for targeting this age range population. One is that there is great concern regarding the development of noise-induced hearing changes in young adults due to their frequent exposure to loud activities (particularly the use of PLD) (Keppler et al., 2015; WHO, 2015). In addition, this age group is most likely to have measurable OAEs (across both CAF and EHFs), at least for the non-noise exposed individuals. Finally, the fewer confounding effects of age on NIHL, the easier it will be to detect NIHL (which is the aim of the study), since other studies have indicated that NIHL and ARHL do not simply add up: in ears that show high ARHL, NIHL appears to be lower, presumably because OHCs can die only once (NIHL is thought to be mainly OHCs at least initially, while ARHL may be a combination of sources of damage) (Gates et al., 2000). All subjects who voluntarily participated in the study had to go through inclusion and exclusion criteria as detailed below. Ethics approval was provided by the Ethics Committee at the UoS (Reference number: 40092.A1).

3.3.2.1 **Inclusion criteria**

Subjects were required to be aged 18 to 35 yrs (inclusive), with no history of ME or hearing impairment, and had to pass initial auditory screening as detailed Table 3.1 below. shows the screening recruitment criteria. One ear was tested; which ear to test was based on CAF-OAEs measured using the ILO 292 in “quickscreen” mode, and the ear with the better overall TEOAE amplitude was selected for further testing. A total of 67 subjects responded to the participant advertisement; five were excluded due to wax impact in ear-canal and two were excluded due to poor CAF-TEOAEs. Three subjects had flat tympanometry, likely due to fluid impact in the ME and were asked to return after three weeks, and of these, only one returned and passed the screening criteria (Figure 3.8).

Table 3.1:The screening criteria for subject inclusion.

Screening	Otoscopic examination	Tympanometry	ILO 292	CAF-HTL
Criteria	EAC clear from discharge, excessive wax, and any obstacle in EAC	-ME compliance: within 0.3 and 1.6 ml -ME pressure: between ± 50 daPa	-Waveform reproducibility ≥ 80% -Rejected epochs ≤10%	HTL for all 7 CAF is 20 dB HL or better
Inclusion	Clear	Normal	Present	≤ 20 dB HL

3.4 Experimental equipment

The following equipment was used for hearing measurements. All the testing was conducted in a soundproof booth in the ISVR building. Measurement of the ambient noise in the booth, when recorded with the sound level meter, was below 35 dB(A).

3.4.1 CAF and EHF Pure Tone Audiometry

The tests were conducted using an in-house software comprising a DELL laptop and RME Babyface Pro soundcard controlled by in-house MATLAB software to collect measurements of hearing threshold levels in the ear. Circumaural headphones were used (Sennheiser HDA200) which have a bandwidth and flat frequency response that makes them eligible to be used for EHF audiometry. HTLs were measured using BSA procedure for CAF of 0.5, 1, 2, 3, 4, 6, and 8 kHz and EHF of 10, 11.2, 12.5, 14, 16, and 18 kHz (BSA 2011) with a 5 dB step size.

Prior to the start of any testing, calibration in the booth was carried out to ensure that the signal delivered by the in-house audiometer via the Sennheiser HDA200 matched the intended stimulus level. The headphones were calibrated using an artificial ear (Bruel and Kjaer [B&K], type 4153), with the flat plate coupler connected to a sound level meter (B&K, type 2250). The obtained measurement of the output was assessed relative to a known standardized hearing threshold RETSPLs (ISO 389-5 2006), which only provided RETSPLs up to 16 kHz. At 18 kHz, a separate analysis was performed due to missing data (Section 3.6.3.1).

3.4.2 CAF-TEOAEs

The CAF-TEOAE recording was the same as that obtained from the screening procedure (Otodynamic ILO292 operated by ILO version 6 software), i.e. click stimulus level 80 dB peSPL and “quickscreen” mode for recording window of 2.5–12.5 ms. This provides measurements in five half-octave bands (nominally centred at 0.7, 1, 1.4, 2, 3, 4, and 5.65 kHz) of the OAE amplitude and SNR.

3.4.3 EHF-TEOAEs

TEOAEs were measured using in-house ISVR software designed specially to record high-frequency OAEs using the Etymotic ER-10B+ probe assembly that comprised a low noise microphone with a preamplifier set at + 20 dB gain, and two ER-2 earphones connected to an RME Babyface Pro driven by MATLAB with a sample rate of 44.1 kHz. Two different stimulus waveforms were used to evoke EHFs OAEs: one a high-pass filtered click (HPF) and one a tone burst centred at 10 kHz (TB). It is worth mentioning that OAEs at CAF were measured using the ILO rather than the in-house equipment because the HPF and TB stimulus paradigms would not strongly evoke OAEs at this frequency range due to the low energy of the stimulus spectrum at CAFs.

3.4.3.1 **Stimulus waveforms**

The HPF stimulus has a cut-off frequency of 4.8 kHz, passing energy above that frequency and attenuating energy below that frequency (Figure 3.1). The purpose of using this stimulus (rather than a standard rectangular 0.1 ms pulse) was to enhance high-frequency TEOAEs without overloading either the hardware or the auditory system, by reducing the stimulation of the low-frequency regions on the BM, which might then suppress the EHF regions. This delivers more energy to the EHF region than is attainable with a standard rectangular (electrical) pulse with the same peak driving voltage. It also reduces the overall subjective loudness of the stimulus (for a given EHF energy) which is more comfortable for the subject. This means that when comparing the HPF click with the standard click for a given amount of the EHF energy in the stimulus, the HPF click will have reduced transducer voltages and displacement of the earphone (as well as reduced subjective loudness). This is expected to lead to reduced stimulus artifacts arising from nonlinear behaviour of the transducers and other system components. The purpose of using TBs as the stimulus was similar: all the stimulus energy is concentrated over a relatively narrow band in the EHF region centred at 10 kHz, meaning that peak transducer voltages are lower for the same EHF energy, as well as producing lower subjective loudness that would arise when energy is presented across all bands simultaneously.

The stimuli were calibrated using a B&K Type 4157 occluded ear simulator (IEC 60318-4 2010), with external ear simulator (DB 2012). The probe microphone was calibrated using a sound level calibrator (B&K, Type 4231).

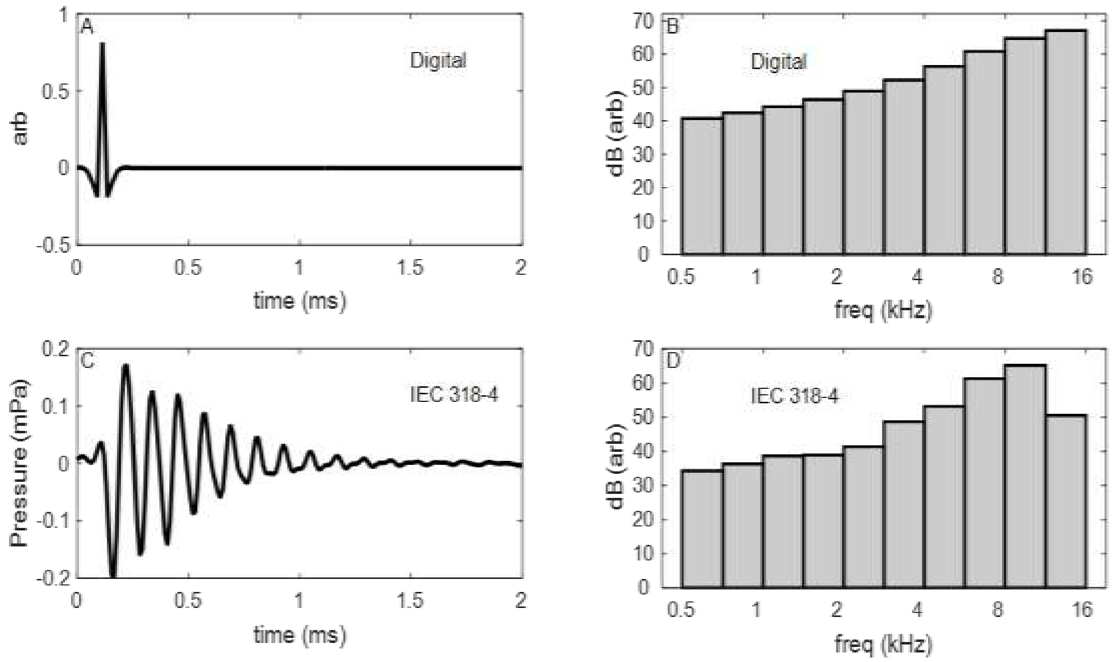


Figure 3.1: Stimulus waveform for high-pass filtered clicks. Upper two panels show the digital waveform in the time-domain (Panal A), and the energy in ½-octave frequency bands (Panel B). The lower two panels (C and D) show the waveform and the energy in ½-octave frequency bands of the acoustic pressure measured in the occluded ear simulator.

3.4.3.2 Double-evoked stimulus paradigm

The double-evoked (DE) paradigm was used to collect the data from both HPF and TB. This technique was described by Keefe and Ling (1998) as a method that derives nonlinear TEOAE responses by using two separate earphones that allows removal of short-latency stimulus artifacts which would otherwise contaminate the EHF-TEOAEs. It allows measurement of the early onset of the response without removing the 2–4 ms latency that contains high-frequency information; with this technique, measurements of high frequencies of more than 5 kHz can be obtained with more reliable results than the conventional ILO paradigm, where the stimulus artifact contaminates signals with latencies of < 3 ms.

This method uses two earphones to derive nonlinear OAE responses (see Section 6.3 and Figure 6.1). DE derives TEOAEs from responses to three stimulus conditions: Earphone 1 alone resulting in Waveform A, followed by a stimulus presented by Earphone 2 alone, resulting in Waveform B, and the third stimulus is a combination of two stimuli from Earphones 1 and 2 presented simultaneously, resulting in Waveform C. The HPF from Earphone 1 is presented at 75 dB peSPL and Earphone 2 stimulus is at 90 dB peSPL. Both waveforms are added, with Waveform C subtracted from them (A+B-C), resulting in a nonlinear residual waveform that is the OAE response.

The measurements were repeated, each resulting in two waveforms of TEOAEs (the A- and B-average waveforms); for each measurement the A and B waveforms were then averaged to provide an estimate of TEOAE signal. During the recording, noisy epochs were rejected with artifact rejection. Table 3.2 shows the EHF hearing measurements. Appendix A demonstrates the DE paradigm in the artificial ear.

Table 3.2: EHF hearing measurements.

Measurements	Test condition	Test Parameters
TEOAEs	HPF TB (10 kHz)	• DE • Artifact rejection was used to reject noisy epochs -Earphone 1;75 dB peSPL -Earphone 2; 90 dB peSPL • The microphone output is filtered to obtain the OAE in ½-octave bands • Two repeated measurements • Recording for 70 sec per measurement.
DPOAEs	8 – 14.1KHz	• 2f1-f2 cubic that results in response of 2 tones • f1/f2 =1.2 • L1 = 70 dB and L2 = 70 dB • L1 = 65 dB and L2 = 55 dB • Two repeated measurements • Recording for 4 minutes (i.e. for the CAF and EHF-DPOAEs) • Measurements were done at these 5 values of f2 8.1, 9.3, 10.7, 12.3 and 14.1 kHz)
PTA	10-18kHz	• BSA procedure • Frequencies tested (0.5, 1, 2, 3, 4, 6, 8, 10, 11.2, 12.5, 14, 16 kHz) • Repeated at 14 kHz • Recording for about 15 minutes

3.4.4 DPOAEs (CAF and EHF)

DP grams were measured using in-house software that was controlled by MATLAB, using the same equipment mentioned in Section 3.4.3. The DPOAE f2-frequency was swept from 1 to 14.1 kHz in frequency steps of 15%. The maximum f2-frequency of 14.1 kHz arises from limitations of the ER-2 earphone, which does not output much energy above 16 kHz. The recording was performed with two primary pure-tones f1 and f2 with two different intensity paradigms of L1 = 70, L2 =70 (denoted 70/70) and L1 = 65 dB, L2 = 55 (denoted 65/55) dB SPL. The measurements were recorded with the frequency ratio f1/f2 = 1.2. The 2f1–f2 DPOAE component was recorded and is shown in Table 3.2.

Calibration of the OAE probe earphones and microphone was carried out before starting the experiment, using the same equipment as for TEOAEs. Both the microphone and earphones for the OAEs equipment were calibrated, to check the microphone function and to ensure that the stimulus levels presented by the two earphones were as intended. The DPOAE measurements to be recorded from the participants were also run in the occluded ear simulator (B&K type 4157) to check if there were any artifactual distortion components generated by system nonlinearity that might be mistaken for genuine DPOAEs arising from cochlear nonlinear responses.

In addition to the full calibrations, before testing each subject, calibration was carried out to check the function of the earphones and the probe microphone. The earphones were calibrated in a hard-wall cavity to verify the intensity level of the stimulus. The probe microphone was calibrated using the B&K sound level calibrator (SLC), type 4230. The procedure was performed by inserting the plastic OAEs probe tip (T11M) into the SLC, which generated a pure tone at 1 kHz and 94 dB SPL.

3.4.5 Noise exposure structured interview (NESI)

As noise exposure is not limited to occupational noise sources, non-occupational sounds can also potentially damage the hearing system. It is unrealistic to quantify the noise exposure level (both occupational and non-occupational) for individuals from the general population with a dosimeter and it is also very difficult to use the sound-level meters for non-occupational exposure. It is also not possible for historical noise exposure. For this reason total noise exposure was estimated using a self-reported interview, that is the NESI (Appendix B), derived from the Noise Exposure and Rating Questionnaire developed by Lutman et al. (2008) and modified by Guest et al. (2018). It has been used for research studies in the UK since the early 1980s. This approach was considered to be more feasible to estimate lifetime noise exposure than other self-reporting questionnaires (Guest et al., 2018).

In general, noise exposure is cumulative; several factors are considered when looking at noise exposure dose: 1) level – "how loud is the noise?"; 2) frequency of occurrence of exposure – "how often is an individual exposed to the noise?"; and 3) duration of each exposure event – "how long is the individual exposed to each occurrence of the noise?". The detailed structured interview used in this study enables the identification of exposure to sound levels that estimated to be > 80 dB (A). Participants provided a detailed history of lifetime noise exposure, covering information about the duration and level of frequent exposure to high level activities, and about the use of personal hearing protection. From this, a metric of individual noise exposure can be estimated.

The NESI, administered by the researcher, consists of three parts and requires approximately 10–20 minutes to be completed. The first section asks for information about engagement in recreational activities with high sound levels. The second section is about occupational noise exposure, and the final part identifies whether the participant has ever engaged in firearms activities.

In the first section, the participant was asked to identify their engagement in activities that are presumably high in sound level (≥ 80 dBA). An example list of the most common recreational noise activities to aid the subject identification of noisy activities is provided in Appendix B. For free field sound levels estimation, the speech communication effort table was used, and the sound levels were estimated and reported on dBA based on the vocal effort required to hold a conversation at a 1.2 m distance. For example, if the subject reported that it was necessary to shout from a distance of four feet to hold a conversation rather than simply raising the voice, an estimate of 99 dBA sound level was recorded. Information about personal hearing protection usage was reported; participants were asked to report the type, attenuation of protector, and proportion of time worn during the activities of exposure. For noise exposure from PLDs, participants reported the typical setting of the volume control on their device, expressed as a percentage of the maximum setting; Appendix B shows the equivalent level in dBA of each percentage. For each activity, the duration of the exposure was estimated by identifying the time period (usually a period of years) during which they have been engaged in the activity. The subject was required to estimate the number of hours per day, days per week, and weeks per year of exposure during the stated period. For the second section, similar questions were asked in related to occupational noise. Completing the NESI form for each participant yielded an estimated level (in dBA) and a duration of exposure for each activity. Ferguson et al. (2019), in assessing the validity of the speech communication effort table, which is a component of the NESI, suggested that the self-reporting table is an effective and reliable tool when comparing estimates to true SPL measured with a dosimeter. Out of 134 subjects, 91% of the estimated noise levels were within ±6 dB, whilst 56% were within ±3 dB. Accordingly, this method has the advantage of providing effective estimation of the noise exposure reported by subjects. Note that the study by Ferguson et al (2019) estimated the exposure to occupational noise only and ignored recreational noise.

To obtain some idea of how the NESI score might relate to predictions of higher noise-induced hearing threshold levels, a comparison can be made to ISO 1999, which estimates the distribution in the population of “noise-induced permanent threshold shift” (NIPTS) for a given continuous noise exposure in dB A, for audiometric frequencies up to 6 kHz (ISO, 1999). The NESI scale is such that 10 units of NESI score would correspond to 10 years of exposure to 90 dBA for 8 hours per day, 5 days per week. For this exposure, ISO 1999 then predicts a median NIPTS of 0, 2, 8, 11, and 7 dB at audiometric frequencies of 1, 2, 3, 4, and 6 kHz respectively. So, for the four frequencies (2, 3, 4, and 6 kHz), the average of the median NIPTS would be 7 dB for a NESI score of 10. This would be the NIPTS relative to an otologically normal (unexposed) ear (Appendix C).

NESI score was used first, because it is straightforward and easy to administer, and second, it is flexible, as reasonable modifications can be made, e.g. if the examiner is interested in studying exposure to noise in the teenage years, they are able to collect information only from that period of time. A third reason is that NESI score has an advantage when used in longitudinal studies, as the baseline reported scores can be recorded and added to follow-up scores. Finally, as reported by Ferguson et al. (2019), the speech communication method has good validity as the objective measurements correspond highly to the self-reported estimates of noise level from the speech communication table.

3.5 Experiment Procedure

The test was conducted in a sound treated booth at the Institute of Sound Vibration. The NESI questionnaire was administered after screening. The participants were seated in a comfortable chair and given clear instructions. HTLs at CAFs and EHFs were measured based on BSA (2011) procedure, CAF-PTA (0.5, 1, 2, 3, 4, 6, 8 kHz). Then the EHF was measured for the frequencies 10, 11.2, 12.5, 14, 16, and 18 kHz. To check each subject’s reliability and level of understanding of the procedure, HTL measurements were repeated at 14 kHz, and most of the time the HTL measurement was repeated with the maximum difference of 5 dB between the test and retest. To keep within the ISVR noise exposure limits, the stimulus tone level was limited to no more than 50 dB HL, or 105 dB SPL (whichever was the lower). For 18 and 16 kHz, when threshold was beyond this exposure limit it was assigned as “no response”.

The recording of TEOAEs and DPOAEs were conducted after instructing the participants to remain quiet and avoid movement during the test. The participants were asked to inform the researcher if the probe tip moved or fell out or if they felt uncomfortable proceeding with the experiment. An appropriately sized probe tip was selected based on the size of each participant's ear canal, to ensure sufficient sealing, reduce probe movement and prevent leakage of sound. After fitting the probe in the subject’s ear-canal, the booth door was closed to reduce ambient noise interference. The tester took the measurements in the observation room.

For the TEOAE tests, the stimulus was presented using the DE paradigm, using MATLAB in order to eliminate stimulus artifacts with high-frequency recording (Keefe, 1998). See Table 3.2 for the measurement parameters. Measurements for the DP gram were also obtained and controlled by MATLAB.

Data was collected as described as previously described in Section 3.4, and statistically analysed using IBM SPSS Statistics version 25.

3.6 Results

3.6.1 Overview

For the TE- and DPOAE measurements, two replicate waveforms were obtained and were averaged to improve the SNR. For TEOAEs, the SNR was estimated from the A and B-waveforms in each frequency band (e.g. Vaden et al., 2018). For DPOAEs the SNR was estimated by estimating the noise using the spectral lines adjacent to that for the DPOAE signal (similar to the method described in ILO V6, 2009). Both the signal amplitude and SNR were calculated to obtain the outcome measured for analysis.

Averages across frequencies were then calculated for the HTLs and OAEs to obtain measures in two frequency ranges: CAF and EHF. These are as following: CAF-HTLs were expressed as 7-frequency average CAF-HTL (i.e. averaged across 0.5, 1, 2, 3, 4, 6, and 8 kHz) and EHF-HTLs were expressed by 5-frequency average EHF-HTL (i.e. averaged across 10, 11.2, 12.5, 14, and 16 kHz). The frequency-averaged HTLs were calculated as the average of the single-frequency HTLs expressed in dB HL.

Frequency-averaged CAF-DPOAEs were calculated over 16 f2-frequencies (i.e. averaged across 1, 1.1, 1.3, 1.5, 1.7, 2, 2.3, 2.6, 3, 3.5, 4, 4.6, 5.3, 6.1, 7, and 8 kHz), while frequency-averaged EHF-DPOAEs were calculated over 4 f2-frequencies (i.e. averaged across 9.3, 10.7, 12.3, and 14.1 kHz). These frequency-averaged DPOAE amplitudes were calculated by averaging the DPOAE amplitudes expressed in Pa^2 (rather than in dB SPL), after which they were converted to dB SPL. This metric therefore gives a measure based on the average acoustic energy over the two ranges. This also avoids the problem that would occur with attempting to average DPOAEs levels expressed in dB SPL, where DPOAE amplitudes at individual frequencies can be below the noise floor, and hence have an estimated level in dB SPL of minus infinity, which cannot be included in an average.

Frequency-averaged CAF-TEOAEs were calculated over 7 ½-octave bands (i.e. averaged across the frequency bands from quick screen ILO, centred at 0.7, 1, 1.4, 2, 2.8, 4, and 5.65 kHz), and frequency-averaged EHF-TEOAEs were calculated over 3 ½-octave bands (i.e. averaged across bands centred at 8, 11.3, and 16 kHz). As with DPOAEs, the frequency-average was calculated over TEOAE band amplitudes expressed in Pa^2 rather than in dB SPL. Note that the EHF range for TEOAEs is defined slightly differently from that for HTLs and DPOAEs because the conventional TEOAE range is typically limited to a maximum of around 6.7 kHz (the upper edge of the 5.65-kHz ½-octave band) or less.

Throughout this thesis, where appropriate, the distribution of a variable was assessed by visual inspection to check that the assumption of normality was reasonable in terms of skewness and extreme outliers (Field. 2009, p. 144-184). Normality has been assumed except where stated, leading to the use of non-parametric statistical tests.

3.6.2 Descriptive statistics

Table 3.3: Number of participants and their mean age, NESI score, and gender.

Category	Included in study
Number of subjects	58
Age, Mean/(SD) (years)	24.1/ (4.5)
Age, Median	23
Number of Male	28
Number of Female	30
Number of subject in UoS music department, Solent Music department, UoS non-music	4, 3, 51
Minimum NESI score	.01
Maximum NESI score	96.11
NESI score, Mean/(SD) (NESI units)	13.8/(18.1)
NESI score Median, (NESI units)	7.1

Table 3.4 shows the mean (across sample) and SD of both the 7-frequency average CAF-HTLs and 5-frequency average EHF-HTLs. Table 3.5 shows the mean and SD of the signal amplitudes and SNRs for CAF-OAEs and EHF-OAEs. HTL is expressed in dB HL, while OAE signal amplitude is expressed in dB SPL, and SNR in dB. Box-and-whisker plots of the HTL properties are shown in Figure 3.2. Note only the DPOAEs at (70/70) and TEOAEs with HPF are included in this section.

Table 3.3: Number of participants and their mean age, NESI score, and gender.

Category	Included in study
Number of subjects	58
Age, Mean/(SD) (years)	24.1/ (4.5)
Age, Median	23
Number of Male	28
Number of Female	30
Number of subject in UoS music department, Solent Music department, UoS non-music	4, 3, 51
Minimum NESI score	.01
Maximum NESI score	96.11
NESI score, Mean/(SD) (NESI units)	13.8/(18.1)
NESI score Median, (NESI units)	7.1

Table 3.4: Mean/(SD) for CAF and EHF-HTL (n=58). Note that the CAF-HTL was averaged over 7 frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) and the EHF was averaged over 5 frequencies (10, 11.2, 12.5, 14, and 16 kHz).

HTL (dB HL)	**Mean**	**SD**
CAF	2.74	2.9
EHF	10.4	10

Table 3.5: Mean /(SD) for CAF-DPOAEs, 16-f2-average (averaged across: 1, 1.1, 1.3, 1.5, 1.7, 2, 2.3, 2.6, 3, 3.5, 4, 4.6, 5.3, 6.1, 7, and 8.1 kHz), EHF-DPOAEs, 4-f2-average (averaged across: 9.3, 10.7, 12.3 and 14.1 kHz), CAF-TEOAEs, 7-band average (averaged for quick screen ILO frequencies: 0.7, 1, 1.4, 2, 2.8, 4, and 5.65 kHz), and EHF-TEOAEs, 3-band average (averaged across 3 frequencies: 8, 11.3 and 16 kHz) (n=58).

DPOAE using (70/70)-paradigm	**Mean**	**SD**
CAF/SNR (dB)	25.7	6.6
CAF/SIGNAL (dB SPL)	22	4.3
EHF/SNR (dB)	21.1	4.5
EHF/SIGNAL (dB SPL)	12.2	4.7
TEOAE using HPF-paradigm	**Mean**	**SD**
CAF/SNR (dB)	22.1	5.6
CAF/SIGNAL (dB SPL)	20.1	5.5
EHF/SNR (dB)	8.39	5.91
EHF/SIGNAL (dB SPL)	7.22	5.73

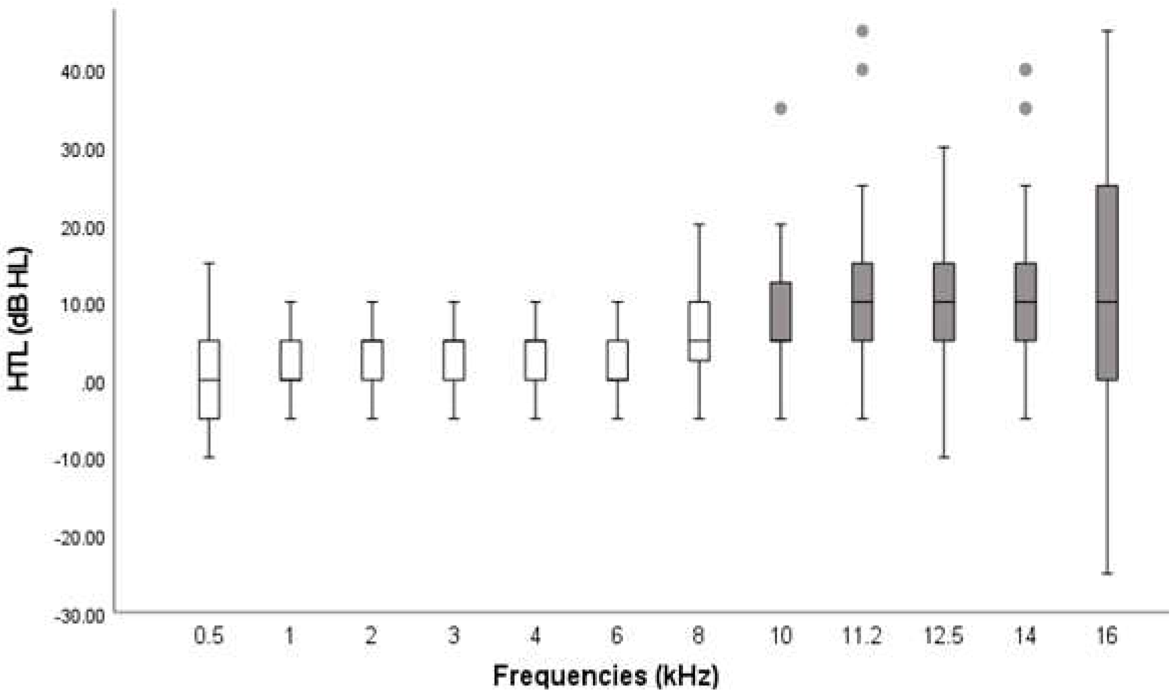


Figure 3.2: Box and whisker plots for HTLs across CAF and EHF ranges. Boxes represent the interquartile range, with the median shown by a horizontal line. Circles indicate minor outliers, defined using fences of 1.5x the interquartile range. Whiskers represent the maximum and minimum values excluding outliers. The white boxplots indicate those values used to calculate the 7-frequency average CAF-HTL, while the grey boxes indicate the values to calculate the 5-frequency average EHF-HTL, n=56 for 16 kHz.

3.6.3 Effect of NESI score on hearing measurements at CAFs and EHFs

This section addresses the research questions RQ 1a and RQ 1b (Section 3.2), that is, evaluation of the impact of noise exposure on hearing, and assessing whether NESI scores have a greater effect on EHF measurements of HTL, DPOAEs, and TEOAEs than CAF-measurements.

The effects of noise exposure (via NESI score) on measurements of hearing status at CAFs and EHFs were assessed statistically in two different ways. The first used LMM with the NESI score as a predictor on a continuous interval scale. The second used a split-plot ANOVA, with the NESI score used to define “high” and “low” noise-exposure groups based on the median NESI score in the sample: i.e. a categorical factor. The reason for performing the two analyses is that each may have its own advantages. For example, benefits of the LMM is that it yields an estimate of the gradient of the hearing measurement vs. NESI score, and does not assume a particular form of the covariance matrix for repeated measures comparisons. However, the LMM treats the NESI score as a continuous predictor variable and may be more susceptible to outliers in the NESI score than would an analysis using a categorical predictor for NESI score. In both analyses, the frequency range over which the measurements are averaged is treated as a within-subject factor with two levels (i.e. CAF and EHF), while age is treated as a covariate.

Figure 3.2 and Table 3.4 show that the inter-subject variability, even in subjects with normal HTL at CAF range, is much higher at EHF than at CAF, as shown previously (Lee et al.; 2012; Rodriguez Valiente et al., 2014; Han and Poulsen, 1998). The intra-subject variability is only slightly poorer at EHF than at CAF, as quantified by Schmuziger et al. (2004). At 16 kHz, 83% of subjects had errors within 5 dB and 98% of subjects had errors within 10 dB. Even though the inter-subject variability is high, it does not make detecting changes over time impossible.

Note that no Bonferroni corrections for multiple tests have been applied for any of the hypothesis tests throughout this thesis, unless this is explicitly stated. For this reason, it is indicated where p-values are <0.05, <0.01 or <0.001 in order indicate the degree of confidence that the result is not a false-positive finding.

3.6.3.1 **Separate analysis at 18 kHz**

The 18 kHz data were excluded from the main analysis in this study (section 3.6.3.2) and were instead analysed separately here. The reason for this was that 11 of the subjects failed to respond to tones at 18 kHz up to 105 dB SPL, which is the tone level limit set by ISVR.

This separate analysis was conducted for the 18 kHz frequency with any non-responses coded as 110 dB SPL (i.e. 5 dB above the maximum allowable level). The data are not normally distributed, therefore a non-parametric test (the Mann-Whitney U test) was done to compare the 18 kHz measurements of the low- NESI group and the high- NESI group. There were no statistically significantly differences between groups (U = 487, p = 0.19).

3.6.3.2 **Effect of NESI score on HTLs at CAFs and EHFs: LMM**

To assess RQ 1a (Section 3.2), an LMM analysis was used to determine (1) whether the NESI score predicts a difference in HTL on average, (2) whether the NESI score has a greater effect in the EHF range than the CAF range, and (3) whether there are effects of age. The model for the analysis was set as following:

$$HTL_{ij} = HTLint_j + \beta_1 \times NESI_i + \beta_2 \times age_i + \beta_3 \times NESI_i \times FreqRange_j + \beta_4 \times age_i \times FreqRange_j + \varepsilon_{ij}$$

where the subscript i is the subject ID (1 to 58); the subscript j is the index of the frequencies range (0 = CAF; 1 = EHF); $FreqRange_j$ is a fixed dummy factor with two levels, and is equal to 0 for CAF and 1 for EHF; $NESI_i$ is a covariate equal to the NESI score for subject i ; age_i is a covariate equal to the age of subject i ; $NESI_i$ x $FreqRange_j$ is an interaction covariate equal to the NESI score multiplied by the $FreqRange_j$; age_i x $FreqRange_j$ is an interaction covariate equal to the age score multiplied by the frequency index; ε_{ij} is the error term; and the β_1 to β_4 terms are the regression coefficients. $HTLint_j$ are the intercepts for the two frequency ranges: the two HTLs over the CAF and EHF ranges estimated for a NESI score of 0 and an age of 0 years. The term ε_{ij} is the residual. The first interaction term allows for any effect of NESI score on HTL to differ in the CAF and EHF regions, while the second allows any effect of age on HTL to differ in the CAF and EHF regions. For example, a positive β_1 indicates how much an increase of 1 NESI unit will increase the HTL by (in dB) over both the CAFs and EHFs, a positive β_2 indicates how much a difference in age of 1 year affects the average HTL over both the CAF and EHF, a positive β_3 would indicate that the NESI score affects the EHF-HTL in addition to the effect accounted for by β_1, and a positive β_4 would indicate that the age affects the EHF-HTL in addition to the age effect accounted for by β_2. The model was run in SPSS using a residual, ε_{ij}, with an unstructured covariance matrix (3 parameters) to allow for correlated residuals across the two frequency ranges, as well as different variances in these two ranges. The criterion for inclusion of parameters in the residual covariance matrix was based on the log-likelihood ratio test (Twisk, 2019).

Before proceeding with the analysis, the Pearson correlation coefficient between the two predictors, i.e. age and NESI score, was calculated and found to be not statistically significant ($R = -0.08$; $p>0.05$). If the two predictors had been strongly correlated, it would be difficult to determine whether any difference in HTL was more associated with age or with NESI score; as this was not the case, this problem did not arise. The lack of correlation was expected due to the relatively young age of the participants.

Table 3.6A shows the results of the LMM with the model, including both NESI score and age as covariates. The effects of age were found to be non-significant, as would be expected given the small range of ages in the sample. Thus, the effect of age was removed from the model. Table 3.6B shows the results of the LMM with the model, including only the NESI score as a covariate, showing little effect of removing age from the model. The results suggest that NESI score has a statistically significant effect on 7-frequency average CAF-HTLs, and a statistically significantly higher effect on 5-frequency average EHF-HTLs than on CAF-HTLs. The significance of including the interaction term (β_3) in the model, indicating a greater effect of NESI score in the EHF range than in the CAF range, was tested using the log-likelihood ratio test (Twisk, 2019).

The between-subject interpretation showed that when two subjects differ by one unit of NESI score, they differ 0.04 in dB for 7-frequency average CAF-HTLs. On the other hand, the within-subject interaction (frequency range) indicates when there is an increase in NESI score of one unit for overall frequency range, there is an increase in HTL by 0.21 dB HL for each subject above the increase in 7-frequency average CAF HTLs.

Figure 3.3 below shows the scatter plot of EHF-HTL vs. NESI score. While there is a discernible trend positive slope, there is also a sparsity of data points with high NESI scores, leading to the potentially large influences of one or two data points on the estimated gradient. For this reason, an analysis was also conducted using the NESI score to define noise exposure categories (Section 3.6.4).

Table 3.6A: LMM model with NESI score and age as covariates, for the relationship between HTL and NESI score, showing the p-values, beta coefficients, and confidence interval (CI).

Effect of NESI score on HTL (dB HL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, β_1	0.25	p<0.05	0.11	0.38
EHF vs. CAF, β_3	0.21	p<0.05	0.08	0.32
Effect of age on HTL				

CAF and EHF, β_2	0.10	0.74	-0.41	0.63
EHF vs. CAF, β_4	0.01	0.88	-0.46	0.50

Table 3.6B: LMM model with NESI score covariates, for the relationship between HTL and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, β_1	0.24	$p<0.05$	0.11	0.38
EHF vs. CAF, β_3	0.21	$p<0.05$	0.08	0.33

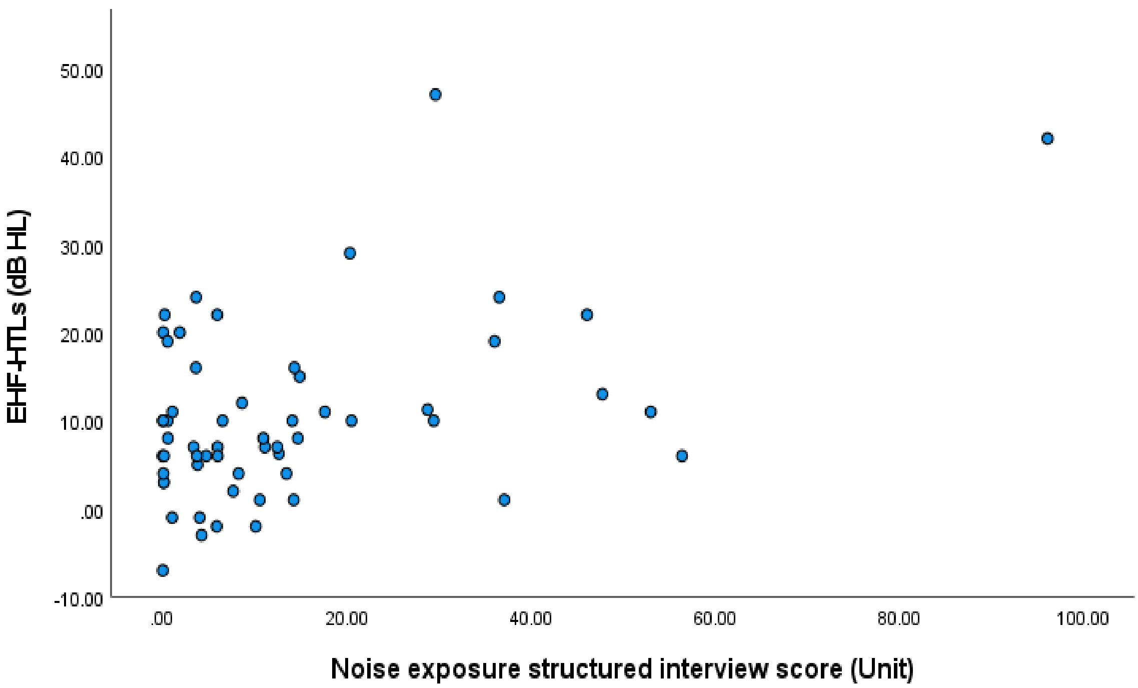


Figure 3.3: Scatterplot of the NESI score and overall EHF HTL 5-average frequency, (averaged across: 10, 11.2, 12.5, 14, and 16 kHz), for the 58 participants. There is a positive trend of correlation between the NESI score and EHF-HTL.

Note that the RQ 1a implies the corresponding null-hypothesis that β_3 is zero, i.e. that the EHF-HTL is affected to the same degree by the NESI score as is the CAF-HTL. The result of the LMM analysis is to reject this null hypothesis as β_3 is significantly different from 0.

3.6.3.3 Effect of NESI score on TEOAE band averages

3.6.3.3.1 Visual inspection of EHF-TEOAEs

Before proceeding with the analysis to answer the research question on the effect of noise exposure on TEOAEs, a visual inspection of waveforms was made with MATLAB.

EHF-TEOAs waveforms were visually evaluated for stimulus artifacts, especially for the early time window that may be contaminated with artifact and contain EHF signals. All data included were subjectively judged to be acceptable. Figure 3.4 shows an example of EHF-TEOAEs measured in one ear of one participant using the DE-paradigm with HPF stimulus, which was judged to be acceptable.

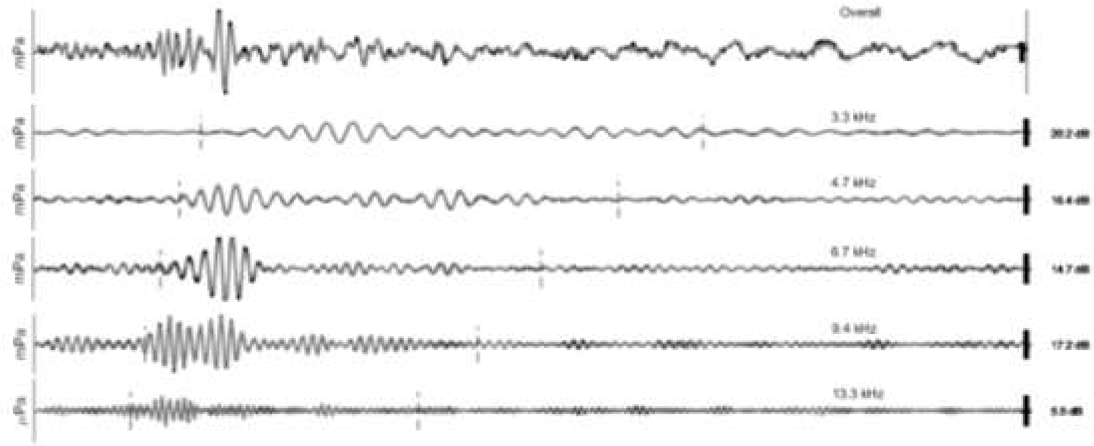


Figure 3.4: Example of TEOAEs measured in Participant 11, using the DE paradigm, evoked using a HPF click stimulus with a stimulus level of 75 dB peSPL. Each trace shows two replicates (one black, one grey) overlaid. The top trace shows the overall signal. The lower five traces show the output after passing the signal through ½ octave filters, with the centre frequency shown above each trace. The time-window over which the TEOAE is analysed is shown by vertical dashed lines. The number in dB on the right-hand side gives the estimated SNR of each trace. Note that only the 3 highest frequency bands (8, 11.3, and 16 kHz) were used to define the EHF-TEOAEs.

3.6.3.3.2 Effect of NESI score on TEOAEs at CAFs and EHFs: LMM

The effect of NESI score on TEOAEs was assessed separately for signal amplitude and SNR. CAF and EHF-TEOAE band-average outcomes were analysed with LMM to determine (1) whether the NESI score predicts a difference in TEOAEs on average, (2) whether the NESI score has a greater effect in the EHF-range than the CAF-range, and (3) whether there are effects of age. The model for the analysis was set as follows:

- TEOAE amplitude $_{ij}$ = TEOAE amplitude int$_j$ + β_1 x NESI$_i$ + β_2 x age$_i$ + β_3 x NESI$_i$ x FreqRange$_j$ + β_4 x age$_i$ x FreqRange$_j$ + ε_{ij}
- TEOAE SNR $_{ij}$ = TEOAE SNR int$_j$ + β_1 x NESI$_i$ + β_2 x age$_i$ + β_3 x NESI$_i$ x FreqRange$_j$ + β_4 x age$_i$ x FreqRange$_j$ + ε_{ij}

for example negative β_1, indicates how much an increase of one NESI unit was associated with a decrease in the average SNR/amplitude over CAFs and EHFs; a negative β_2 indicates how much a difference of one year of age affects average SNR/amplitude over CAFs and EHFs; a negative β_3 would indicate that the NESI score affects the EHF amplitude/SNR in addition to the effect accounted for by β_1, and a negative β_4 would indicate that age affects the EHF amplitude/SNR in addition to the age effect accounted for by β_2. The LMM analysis was performed in the same way as for HTLs in (Section 3.6.3.2).

Table 3.7A and A show LMM results; the former shows the amplitude, and the latter shows SNR, with a model including NESI score and age as covariates; the effects of age were found to be non-significant. Therefore, a model for LMM was conducted without including age as a covariate, and only using NESI as covariate (Table 3.7B and 3.8B). The results suggest that NESI score has a statistically significant effect on CAF-and EHF-TEOAE amplitudes and SNR, with no statistically significantly difference in effect of NESI score on EHF-TEOAEs than CAF-TEOAEs. (i.e. EHF-TEOAEs and CAF-TEOAEs are likely to be equally affected by NESI score). Figure 3.5A and B shows the correlation between NESI score and EHF-TEOAEs.

The between-subject interpretation showed that when two subjects differ by one unit of NESI score, they differ by 0.08 dB for SPL and 0.07 dB for CAF- TEOAE amplitude and SNR.

Table 3.7A: LMM model with NESI score and age as covariates, for the relationship between TEOAE amplitude (HPF) and NESI score, showing p-values, beta coefficients and CI.

Effect of NESI score on TEOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta 1$	-0.15	p<0.05	-0.23	-0.07
EHF vs. CAF, $\beta 3$	-0.07	0.13	-0.22	0.16
Effect of age on TEOAE amplitude (dB SPL)				
CAF and EHF, $\beta 2$	-0.09	0.55	-0.40	0.21
EHF vs. CAF, $\beta 4$	-0.05	0.75	-0.42	0.31

Table 3.7B: LMM model with only NESI score as the covariate, for the relationship between TEOAE amplitude (HPF) and NESI score, showing p-values, beta coefficients and CI.

Effect of NESI score on TEOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta 1$	-0.15	p<0.05	-0.22	-0.07
EHF vs. CAF, $\beta 3$	-0.07	0.12	-0.020	0.16

Table 3.8A: LMM model with NESI score and age as covariates for the relationship between TEOAE SNR (HPF) and NESI score, showing the p-values, beta coefficients and CI.

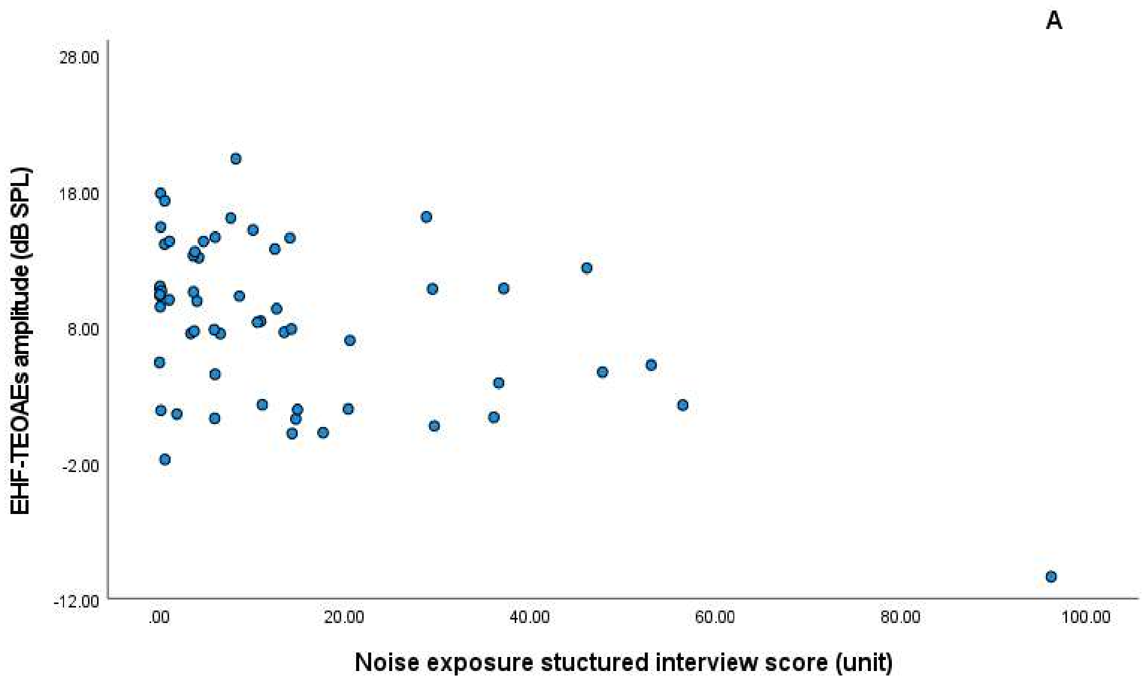
Effect of NESI score on TEOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**

CAF and EHF, $\beta1$	-0.14	P<0.05	-0.22	-0.07
EHF vs. CAF, $\beta3$	-0.08	0.14	-0.02	0.17
Effect of age on TEOAE SNR (dB)				
CAF and EHF, $\beta2$	-0.14	0.33	-0.44	0.15
EHF vs. CAF, $\beta4$	-0.01	0.95	-0.41	0.39

Table 3.8B: LMM model with only NESI score as the covariate, for the relationship between TEOAE SNR (HPF) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on TEOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.14	P<0.05	-0.22	-0.07
EHF vs. CAF, $\beta3$	-0.08	0.12	-0.023	0.17

Unlike the HPF TEOAEs, the results for the TB-10kHz TEOAE paradigm were not analysed using the LMM, but are discussed in Section 3.6.5.



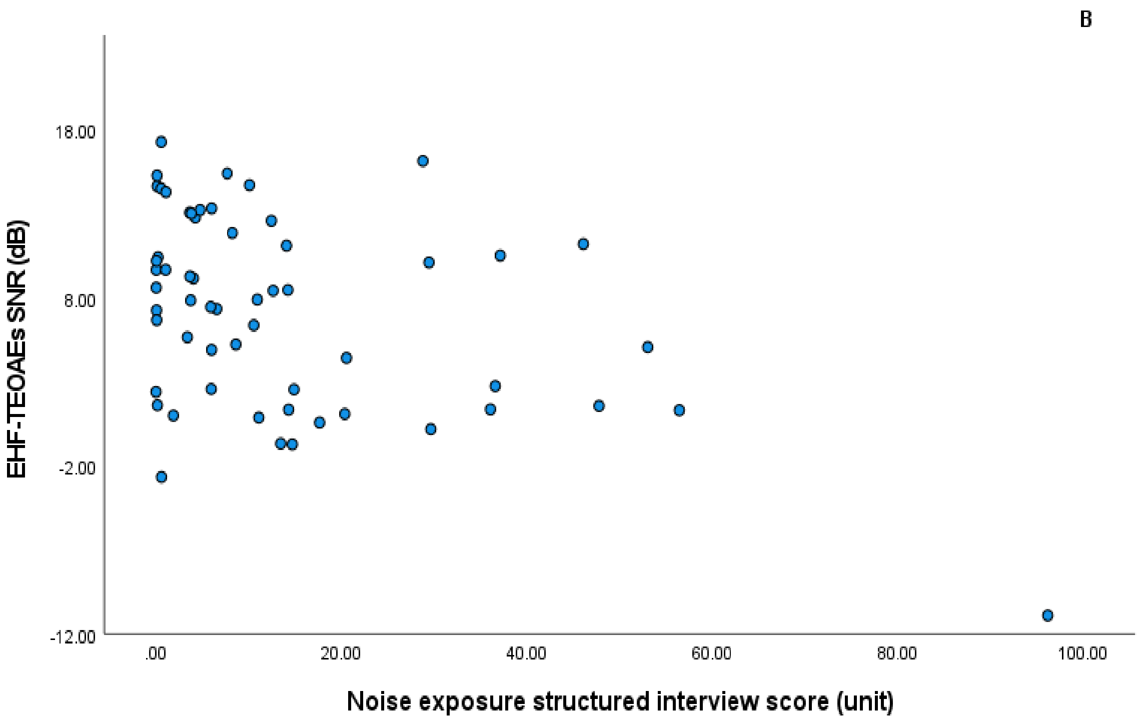


Figure 3.5: Scatterplot of the NESI score and EHF-TEOAEs (using HPF), frequency average across a 3-band average (i.e. averaged across 8, 11.3, and 16 kHz). (A) shows the signal amplitude (dB SPL), and (B) the SNR (dB).

For RQ 1a, the hypothesis that β_3 is not zero, i.e. that the EHF-TEOAEs (HPF-paradigm) are affected to a greater degree by the NESI score than the CAF-TEOAE cannot be accepted from the results of the LMM analysis.

3.6.3.4 Effect of NESI score on DPOAEs at CAFs and EHFs: LMM

Similar to the TEOAE analysis, EHF-DPOAEs were evoked using two stimulus paradigms, i.e. high stimulus level [70/70] and low level [65/55]). This section covers the LMM analysis for the high stimulus level (70/70), the low level (65/55) analysis is covered in Section 3.6.

The effect of noise exposure on DPOAEs was done separately, on the impact on amplitude (dB SPL) and on SNR (dB). LMM was used to determine (1) whether the NESI score predicts a difference in DPOAEs on average, (2) whether the NESI score is a better predictor in the EHF range than the CAF-range, and (3) whether there are effects of age. The model for the analysis was set as following:

- DPOAE amplitude $_{ij}$ = DPOAE amplitude int_j + β_1 x $NESI_i$ + β_2 x age_i + β_3 x $NESI_i$ x $FreqRange_j$ + β_4 x age_i x $FreqRange_j$ + ε_{ij}
- DPOAE SNR $_{ij}$ = DPOAE SNR int_j + β_1 x $NESI_i$ + β_2 x age_i + β_3 x $NESI_i$ x $FreqRange_j$ + β_4 x age_i x $FreqRange_j$ + ε_{ij}

for instance, negative β_1 indicates how much an increase of 1 NESI unit decreases the average SNR/amplitude over CAF- and EHF-DPOAEs; a negative β_2 indicates how much a difference of 1 year of age affects the average SNR/amplitude over CAF- and EHF-DPOAEs; a negative β_3 would indicate that the NESI score affects the EHF-DPOAE amplitude/SNR in addition to the effect accounted for by β_1, and a negative β_4 would indicate that age affects the EHF-DPOAE amplitude/SNR in addition to the age effect accounted for by Beta2. The LMM analysis was performed in the same way as for HTLs in Section3.6.3.2.

Table 3.9A and 3.10A shows the results of LMM, with NESI score and age as covariates in the model. The former table shows the amplitude and the latter shows SNR; effects of age were found to be non-significant. Thus, a model for LMM was conducted including only NESI score as covariate (Tables 3.9B and 3.10B). The results suggest that NESI score has a statistically significant effect on both CAF-and EHF-DPOAE amplitude, with no statistically significantly difference in effect of NESI score on EHF-DPOAEs than CAF-DPOAEs (i.e. EHF-DPOAEs and CAF-DPOAEs are likely to be equally affected by NESI score). Table 3.10 show that NESI score has no statistically significant effect on SNR either for CAF-DPOAEs or EHF-DPOAEs. Figure 3.6A and B show the association between NESI score and EHF-DPOAEs.

The between-subject interpretation showed that when two subjects differ by one unit of NESI score they differ by 0.09 in dB SPL for CAF-DPOAE amplitude.

Table 3.9A: LMM model with NESI score and age as covariates, for the relationship between DPOAE amplitude (70/70 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta 1$	-0.09	P< 0.05	-0.15	-0.03
EHF vs. CAF, $\beta 3$	0.001	0.96	-0.06	0.067
Effect of age on DPOAE amplitude (dB SPL)				
CAF and EHF, $\beta 2$	-0.20	0.88	-0.28	0.24
EHF vs. CAF, $\beta 4$	-0.12	0.34	-0.38	013

Table 3.9B: LMM model with only NESI score as the covariate, for the relationship between DPOAE amplitude (70/70 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.08	P<0.05	-0.15	-0.02
EHF vs. CAF, $\beta3$	0.001	0.97	-0.06	0.06

Table 3.10A: LMM model with NESI score and age as covariates, for the relationship between DPOAE SNR (70/70 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.04	0.30	-0.10	0.03
EHF vs. CAF, $\beta3$	-0.09	0.06	-0.18	0.005
Effect of age on DPOAE SNR (dB)				
CAF and EHF, $\beta2$	-0.008	0.95	-0.27	0.25
EHF vs. CAF, $\beta4$	-0.28	0.13	-0.64	0.09

Table 3.10B: LMM model with only NESI score as covariate, for the relationship between DPOAE SNR (70/70 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.04	0.30	-0.10	0.03
EHF vs. CAF, $\beta3$	-0.08	0.08	-0.18	0.01

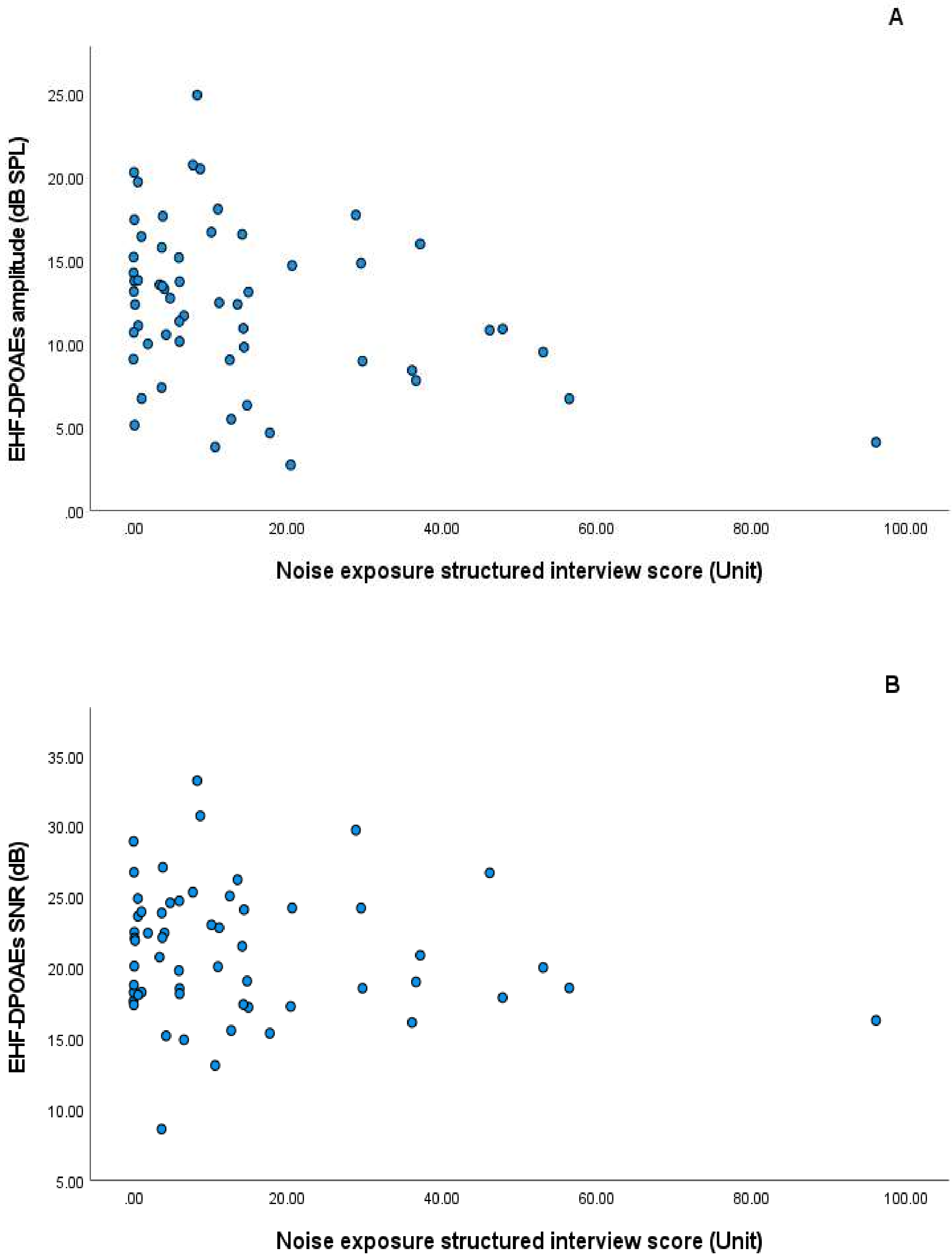
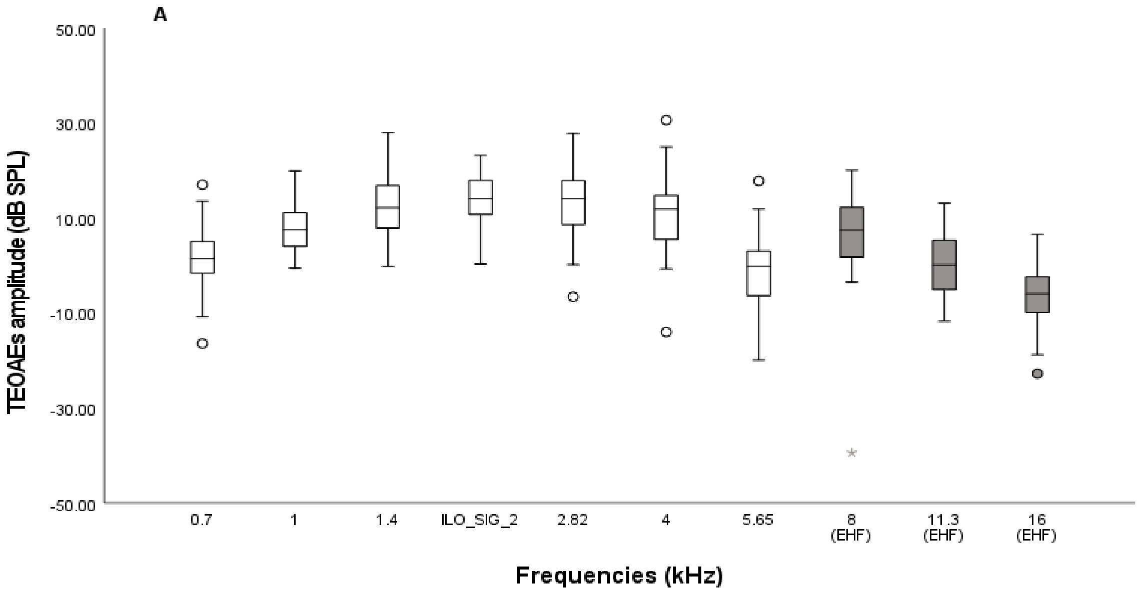


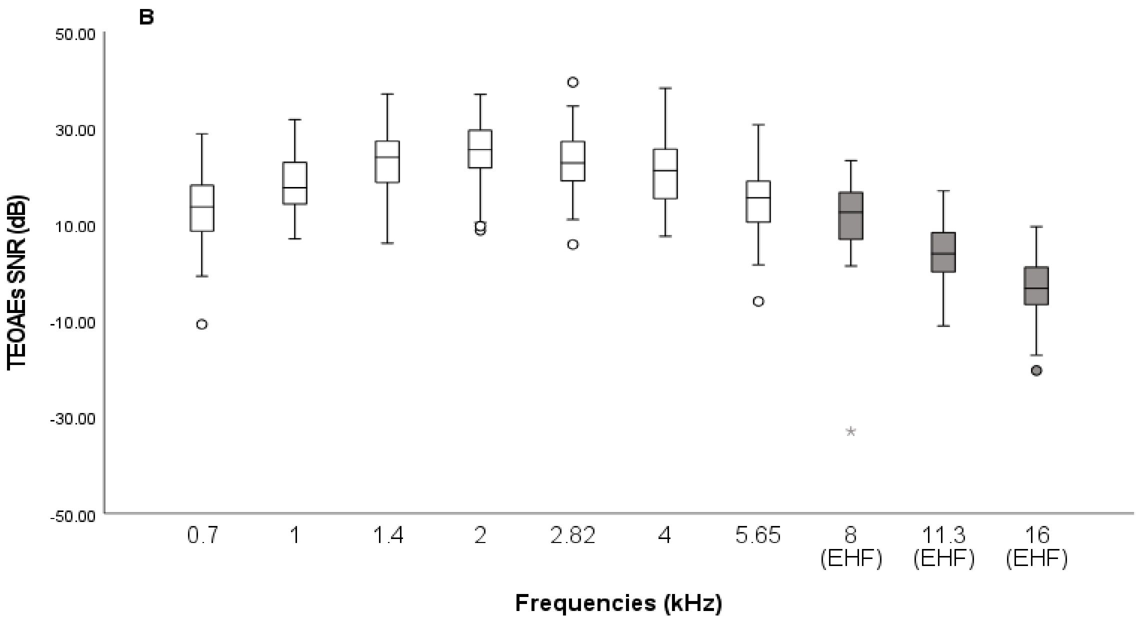
Figure 3.6: Scatterplot of the NESI score and EHF-DPOAE (using 70/70 paradigm) 4-f2 average (i.e. averaged across 9.3, 10.7, 12.3, and 14.1 kHz). (A) shows the amplitude (dB SPL) and (B) the SNR (dB).

For RQ 1a, the hypothesis that β_3 is not zero, i.e. that the EHF-DPOAEs (70/70 paradigm) are affected to a greater degree by the NESI score than the CAF-DPOAE cannot be accepted from the results of the LMM analysis.

3.6.3.4.1 Descriptive for OAEs in ½-octave bands.

Figure 3.7A and B: boxplots of TEOAE amplitude and SNR. The figure shows the median signal amplitudes and SNRs in the ½-otctave bands. Figure 3.7C and D show the box plots for DPOAE amplitude and SNR.





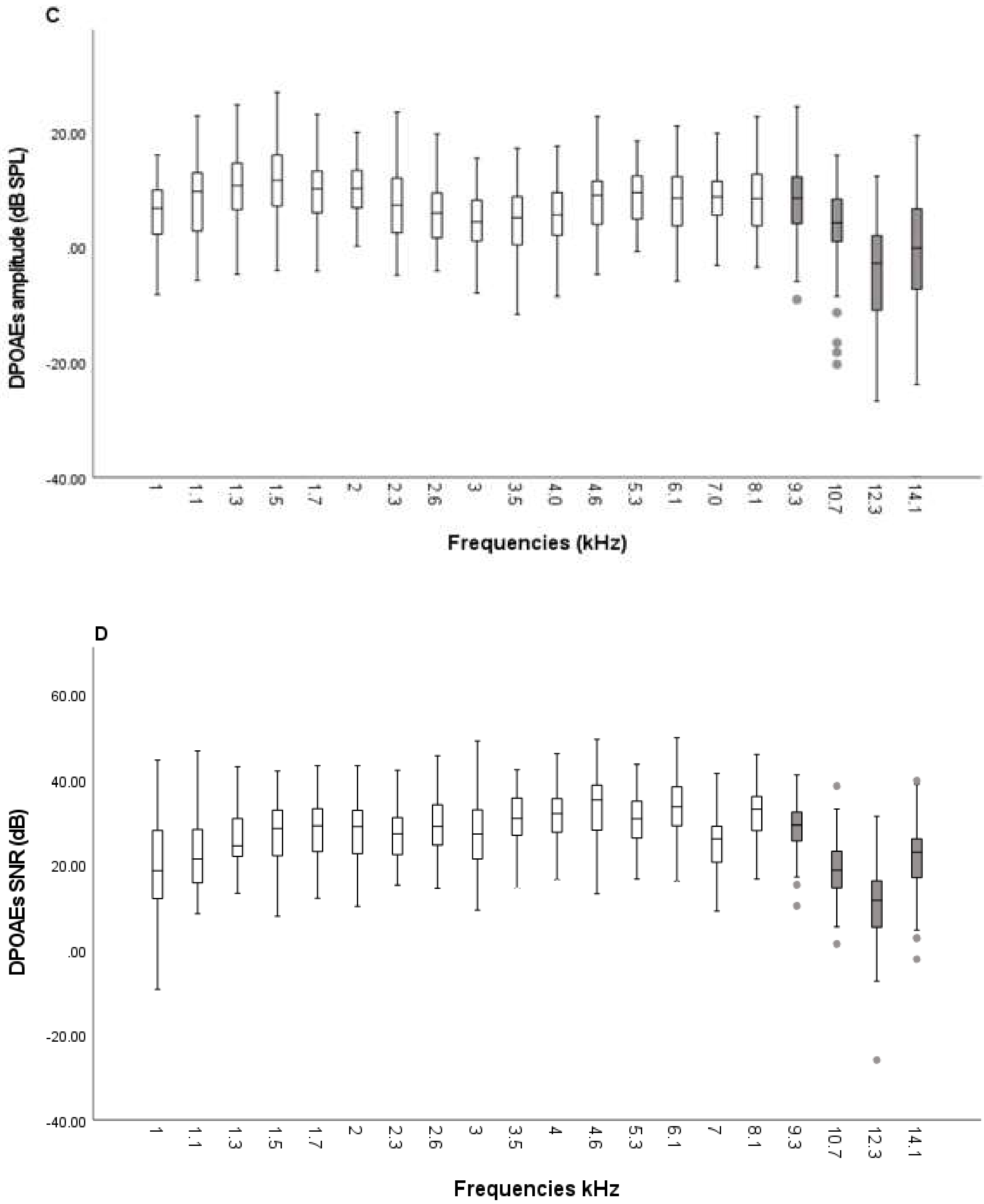


Figure 3.7: Box and whisker plots for TEOAEs using HPF stimulus and DPOAEs using (70/70) stimulus, in ½-octave bands (centre frequency of each band indicated on horizontal axis). Boxes represent the interquartile range, with the median shown by a horizontal line. Circles indicate minor outliers, defined using fences 1.5 times the interquartile range. Whiskers represent the maximum and minimum values excluding outliers. (A) shows TEOAE amplitudes; white boxes are the CAF-TEOAE 7-band averages (i.e. from ILO), while grey boxplots represent the EHF-TEOAE amplitude 3-band averages. (B) shows the SNR of TEOAEs corresponding to the measurements described for (A). (C) shows the DPOAE amplitudes; the grey boxplots indicate those values calculated from 4-frequency average EHF-DPOAEs, while the white boxes indicate the CAF averaged across 16 frequencies. (D) shows the SNR of DPOAEs corresponding to the measurements described for (A)

3.6.3.4.2 Correlation between noise exposure and (65/55) EHF-DPOAEs

Although the results of the paired t-test found that the (70/70) EHF-DPOAEs showed greater amplitude and SNR than the (65/55) (Section 3.6.5), larger correlation coefficients between EHF-HTL and EHF-DPOAEs (65/55) were found for both amplitude and SNR (Table 3.16, section 3.6.6). The effect of NESI score on CAF and EHF DPOAEs was therefore also tested for 65/55 paradigm using the LMM analysis to assess RQ 2a.

Table 3.11A and 3.12A shows the results of LMM, with NESI score and age as a covariates in the model. The former table shows the amplitude, and the latter shows SNR. The effects of age were found to be non-significant. Thus, a model for LMM was conducted with NESI score as the only covariate (Table 3.11B and 3.12B). The results suggest that NESI score has a statistically significant effect on CAF-and EHF-DPOAE amplitude, with no statistically significantly additional effect on EHF-DPOAEs (i.e. the data do not show that EHF-DPOAEs and CAF-DPOAEs are affected by NESI score to a different degree at the 5% level of significance). Table 3.12 shows that NESI score has a statistically significant effect on CAF-DPOAE SNR, but no statistically significant additional effect on EHF-DPOAEs.

The between-subject interpretation showed that when two subjects differ by one unit of NESI score, they differ by 0.10 in dB SPL for both CAF and EHF-DPOAE amplitude. Table 3.12A showed that $\beta 4$ was statistically significant, suggesting that age has an effect on EHF-DPOAEs (65/55) SNR. However, there were no similar effect of age seen on the signal DPOAEs (65/55) amplitude and the EHF-DPOAEs (70/70) for SNR or for signal amplitude. This was not expected given the restrictions on age in the inclusion criteria. EHF-DPOAEs (65/55) SNR was the only variable of the four EHF-DPOAE variables tested that showed as statistically significant effect of age.

Table 3.11A: LMM model with NESI score and age as covariates, for the relationship between DPOAE amplitude (65/55 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.17	P< 0.05	-0.26	-0.09
EHF vs. CAF, $\beta3$	0.06	0.11	-0.015	0.14
Effect of age on DPOAE amplitude (dB SPL)				
CAF and EHF, $\beta2$	-0.08	0.59	-0.42	0.24
EHF vs. CAF, $\beta4$	-0.13	0.37	-0.44	0.16

Table 3.11B: LMM model with only NESI score as the covariate, for the relationship between DPOAE amplitude (65/55 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE amplitude (dB SPL)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.17	P<0.05	-0.26	-0.09
EHF vs. CAF, $\beta3$	0.065	0.97	-0.12	0.14

Table 3.12A: LMM model with NESI score and age as covariates, for the relationship between DPOAE SNR (65/55 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.15	P< 0.05	-0.24	-0.07
EHF vs. CAF, $\beta3$	0.05	0.36	-0.05	0.15
Effect of age on DPOAE SNR (dB)				
CAF and EHF, $\beta2$	-0.08	0.59	-0.42	0.24
EHF vs. CAF, $\beta4$	-0.49	P<0.05	-0.90	-0.08

Table 3.12B: LMM model with only NESI score as the covariate, for the relationship between DPOAE SNR (65/55 paradigm) and NESI score, showing the p-values, beta coefficients and CI.

Effect of NESI score on DPOAE SNR (dB)	**Beta coefficients**	**P-value**	**95% CI (dB HL)**	
			min	**max**
CAF and EHF, $\beta1$	-0.15	P<0.05	-0.23	-0.06
EHF vs. CAF, $\beta3$	0.06	0.29	-0.05	0.16

3.6.4 Comparison of HTLs and OAE responses between high- NESI and low- NESI group based on NESI score: Split-plot ANOVA.

As explained in Section 3.6.3, the effect of NESI score on hearing measurements was assessed using the NESI score as a categorical predictor rather than a covariate, in part to mitigate against the effect of outliers seen in the distribution of NESI scores. In answering the research question (RQ 1b, Section 3.2) on comparing the difference in EHF measures (i.e. HTL, DPOAEs using (70/70), and TEOAEs using HPF) between the low and high noise exposure groups, it was hypothesised that the high NESI group would have worse hearing. A split plot ANOVA was performed to allow comparison between groups (NESI score between participants factor) and to assess the interaction term between CAF and EHF (frequency range within subject factor). The difference between LMM and this analysis is that in the earlier one, noise exposure (NESI score) was treated as a covariate, while in the later test it is regarded as a fixed factor, categorical factor with two levels (high- and low-NESI score).

The ANOVA was used to assess the impact of noise exposure on the hearing of young adults; each subject was assigned to a low-NESI group or high- NESI group based on their NESI score. A NESI score cut-off point for group classification (raw score of 7.69 NESI units) was decided based on the median NESI score. NESI scores of under 7.69 placed participants in the low-NESI group, and if scoring higher than 7.69, they were assigned to the high-NESI group (Figure 3.8). Age is considered as the covariant variable, to account for any impact of age on HTL. Table 3.13 shows details on the median, mean and SD of each group. It can be seen that high- NESI group have higher NESI scores with a wider distribution range of score than the low-NESI group.

Table 3.13: shows the NESI score median and mean/(SD) of the low-NESI and high- NESI groups

Group	Number of subjects	Median	Mean/(SD)
Low- NESI	29	1.08	2.35/(2.34)
High- NESI	29	14.89	25.30/(19.82)

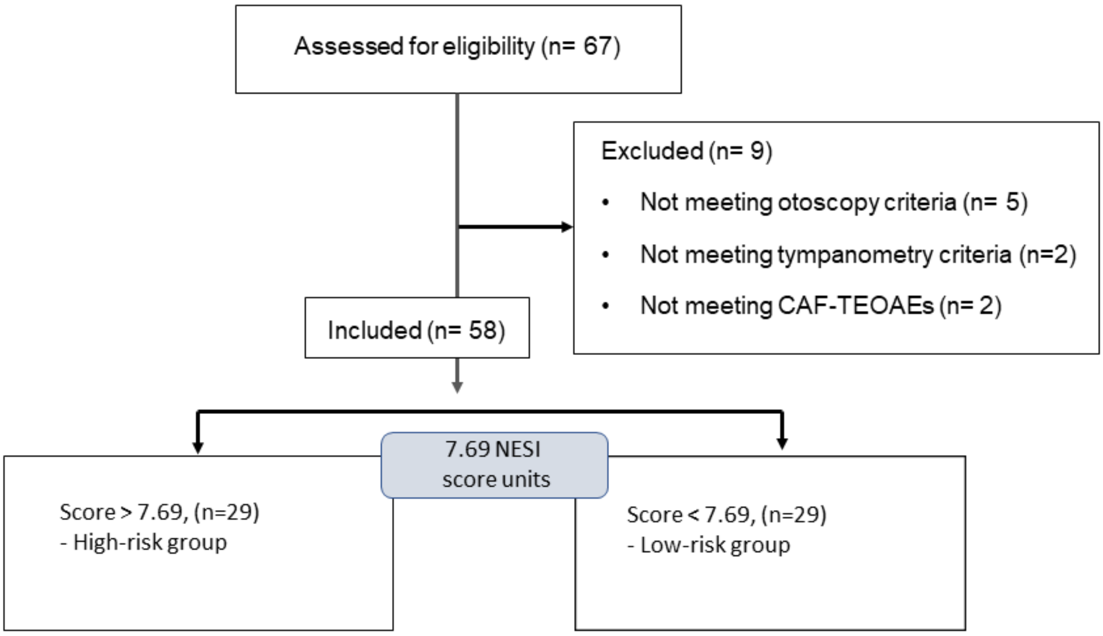


Figure 3.8: Consort diagram showing participant exclusion and inclusion in the study, and subject assignment to analysis groups for split-plot ANOVA. Based on 50 percentile NESI score.

A split-plot ANOVA with age as covariate was used to analyse the effect of NESI on low and high-NESI groups, with NESI score as the IV and HTL as the DV.

Split-plot ANOVA models for analysis were conducted as follows:

- HTL_{ijk} = HTLint + α_0 (FreqRange$_j$) + α_1 (NESI$_k$)+ α_2(NESI$_k$, FreqRange$_j$) + β_2 x age$_i$ + β_4 (FreqRange$_j$)x age$_i$ + ε_{ijk}
- TEOAE amplitude $_{ijk}$ = TEOAE amplitude int + α_0 (FreqRange$_j$) + α_1 (NESI$_k$)+ α_2(NESI$_k$, FreqRange$_j$) + β_2 x age$_i$ + β_4 (FreqRange$_j$)x age$_i$ + ε_{ijk}
- TEOAE SNR $_{ijk}$ = TEOAE SNR int + α_0 (FreqRange$_j$) + α_1 (NESI$_k$)+ α_2(NESI$_k$, FreqRange$_j$) + β_2 x age$_i$ + β_4 (FreqRange$_j$)x age$_i$ + ε_{ijk}
- DPOAE amplitude $_{ijk}$ = DPOAE amplitude int + α_0 (FreqRange$_j$) + α_1 (NESI$_k$)+ α_2(NESI$_k$, FreqRange$_j$) + β_2 x age$_i$ + β_4 (FreqRange$_j$)x age$_i$ + ε_{ijk}
- DPOAE SNR $_{ijk}$ = DPOAE SNR int + α_0 (FreqRange$_j$) + α_1 (NESI$_k$)+ α_2(NESI$_k$, FreqRange$_j$) + β_2 x age$_i$ + β_4 (FreqRange$_j$)x age$_i$ + ε_{ijk}

where i is the subject index (1-58), α_0 is the main effect of frequency range (two levels: CAF or EHF; indexed by j), α_1 is the main effect of NESI group (two levels based on upper or lower 50% percentile; indexed by k, which is determined by the NESI score of subject i), α_2 is the interaction between NESI group and frequency range, β_2 is the coefficient of the age covariate as a main effect, β_4 is the interaction term between the coefficient of the age covariate and the frequency range, and ε_{ijk} is the residual. Split plot analysis for TEOAEs and DPOAEs were performed in the same way as for HTLs, but with SNR and amplitude (TEOAEs and DPOAEs), each analysed separately.

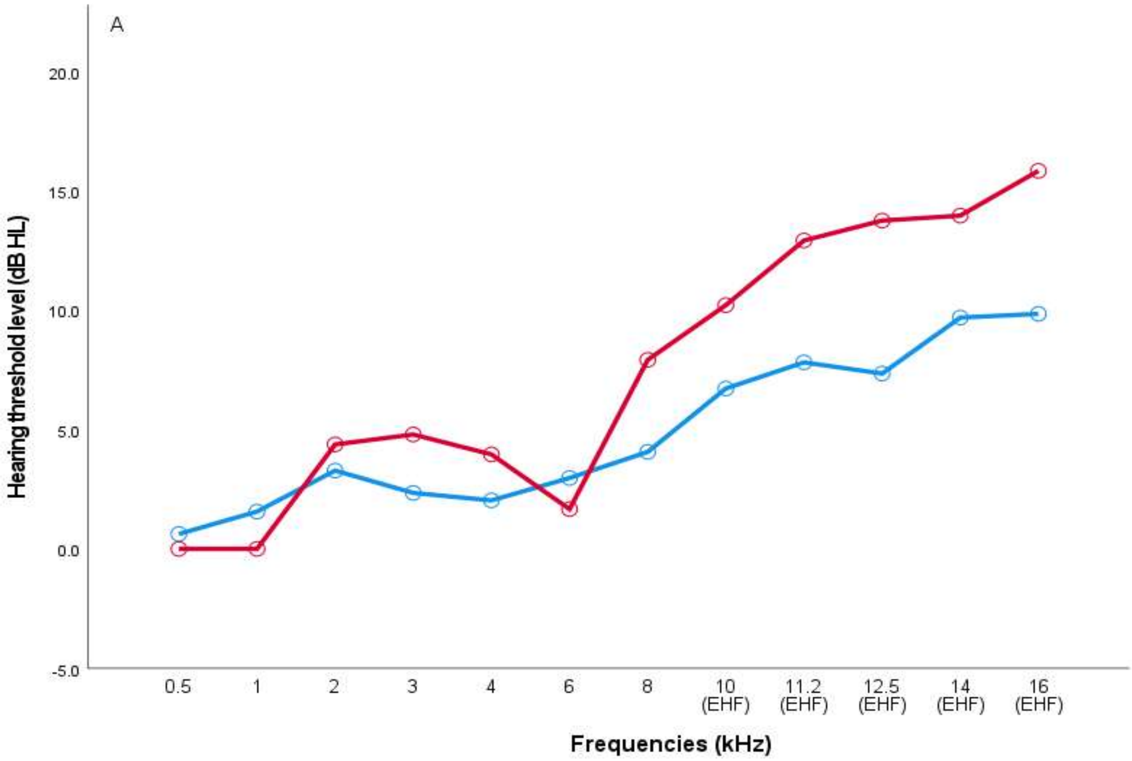
For HTL there was no significant main effect of NESI group (α_1 coefficient) Nor was there a statistically significant interaction between frequency range and NESI group (α_2 coefficient). Figure 3.9A shows the HTL against frequency in the two NESI group. Age was found not to have a significant effect on hearing status (CAF and EHF) for all of the hearing measurements.

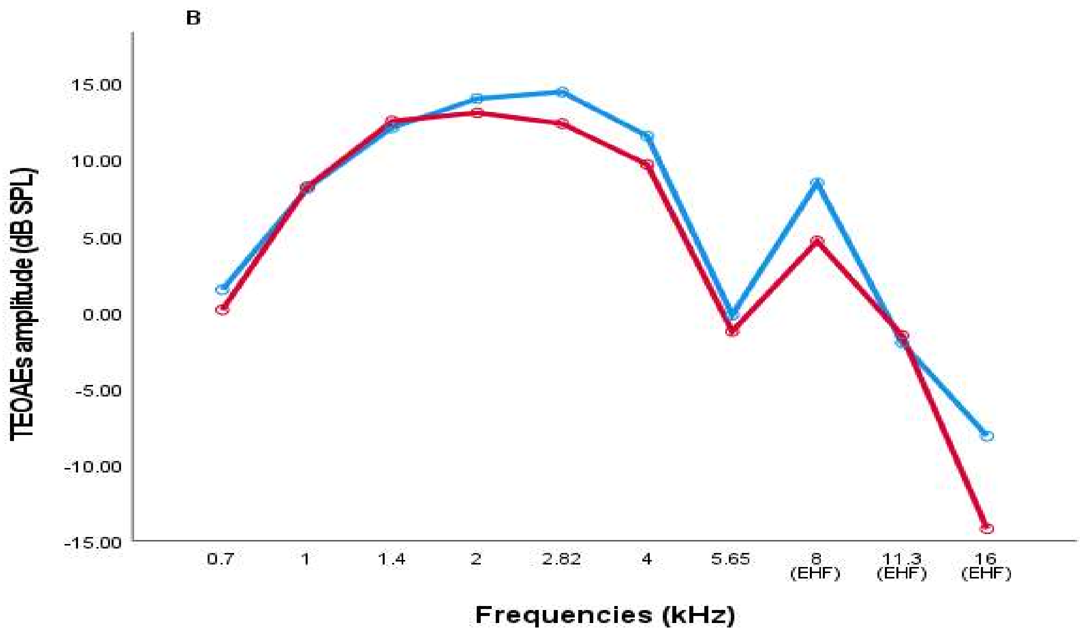
Similarly, no significant main effect of NESI group (α_1 coefficient) for the EHF-DPOAE and EHF-TEOAEs amplitude and SNR, either no statistically significant interaction between frequency range and NESI group (α_2 coefficient). Figure 3.9B and C show the EHFs OAE against frequency for the low- and high-NESI groups. Table 3.14 shows the interaction term between groups and frequency range.

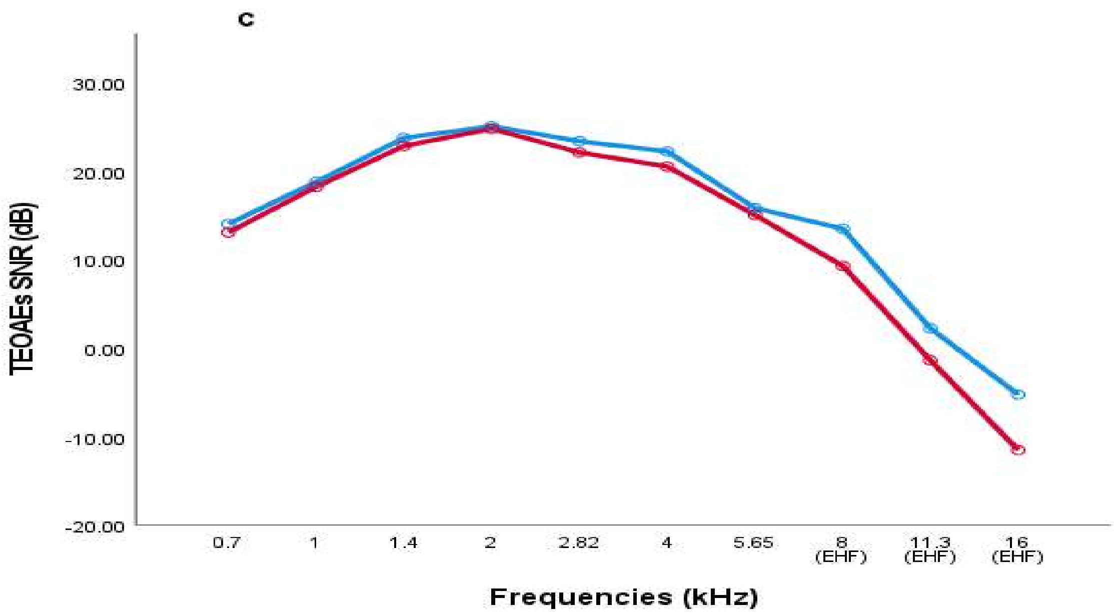
Table 3.14: Mean/SD for high and low NESI groups, for all the CAF and EHF measurements, and interaction term between groups and between frequencies (split-plot ANOVA).

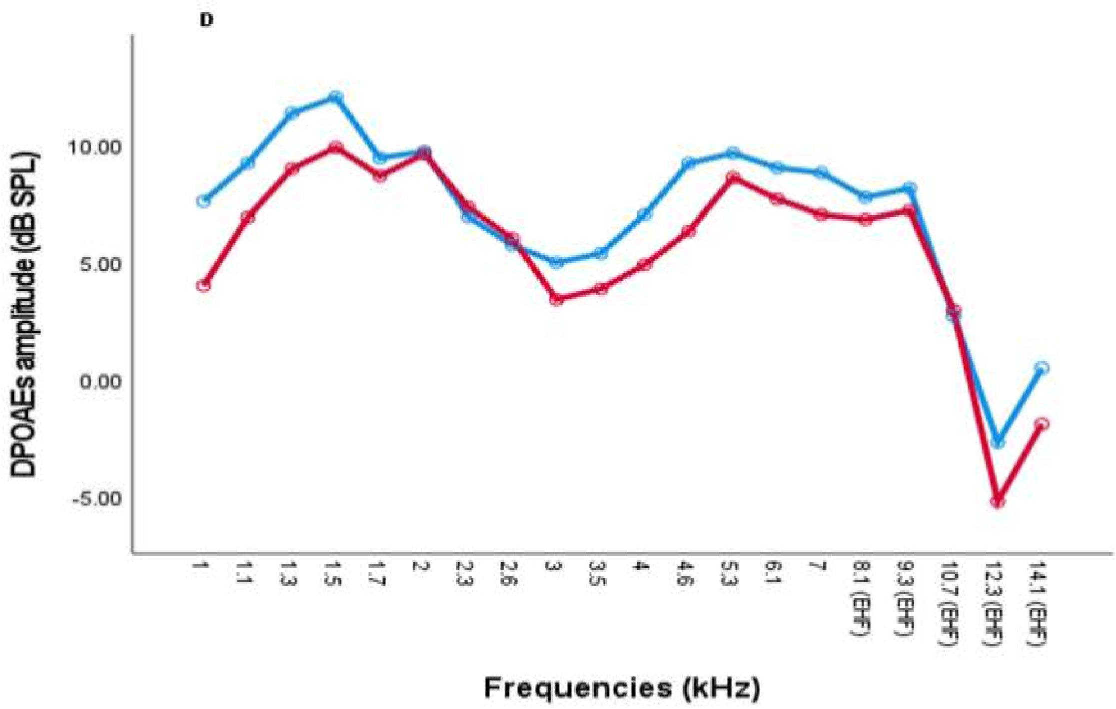
Measurement	**Low NESI (n=29)**		**High NESI (n=30)**		**Simple effects[1]: High NESI group – low NESI group Mean difference dB**	**Interaction term between freq range and NESI group**
	Mean	**±SD**	**Mean**	**±SD**		
CAF-HTL (dB HL)	**2.66**	**3.47**	**2.83**	**2.37**	**0.17**	**3.57**
EHF-HTL (dB HL)	**8.51**	**8.11**	**12.25**	**11.46**	**3.74**	
CAF-DPOAEs Amplitude (dB SPL)	**22.36**	**3.61**	**21.70**	**4.93**	**-0.66**	**-0.61**
EHF- DPOAEs (70/70) Amplitude (dB SPL)	**12.91**	**3.56**	**11.64**	**5.63**	**-1.27**	
CAF-DPOAEs SNR (dB)	**26.38**	**5.73**	**25.05**	**7.54**	**-1.33**	**1.78**
EHF- DPOAEs (70/70) SNR (dB)	**20.89**	**4.22**	**21.34**	**4.96**	**0.45**	
CAF-TEOAEs Amplitude (dB SPL)	**20.56**	**5.12**	**19.74**	**5.98**	**-0.82**	**-3.58**
EHF- TEOAEs HPF Amplitude (dB SPL)	**9.77**	**4.92**	**7.01**	**6.55**	**-2.76**	
CAF-TEOAEs SNR (dB)	**22.66**	**5.84**	**21.58**	**5.59**	**-1.08**	**-4.43**
EHF-TEOAEs HPF SNR (dB)	**8.93**	**4.87**	**5.50**	**6.09**	**-3.43**	

Note[1]: none of the interaction terms was statistically significant, therefore simple effects were not tested statistically.


A
Hearing threshold level (dB HL)
20.0
15.0
10.0
5.0
0.0
-5.0
0.5
1
2
3
4
6
8
10 (EHF)
11.2 (EHF)
12.5 (EHF)
14 (EHF)
16 (EHF)
Frequencies (kHz)


B
TEOAEs amplitude (dB SPL)
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
0.7
1
1.4
2
2.82
4
5.65
8 (EHF)
11.3 (EHF)
16 (EHF)
Frequencies (kHz)


C
TEOAEs SNR (dB)
30.00
20.00
10.00
0.00
-10.00
-20.00
0.7
1
1.4
2
2.82
4
5.65
8 (EHF)
11.3 (EHF)
16 (EHF)
Frequencies (kHz)


D
DPOAEs amplitude (dB SPL)
10.00
5.00
0.00
-5.00
1
1.1
1.3
1.5
1.7
2
2.3
2.6
3
3.5
4
4.6
5.3
6.1
7
8.1 (EHF)
9.3 (EHF)
10.7 (EHF)
12.3 (EHF)
14.1 (EHF)
Frequencies (kHz)

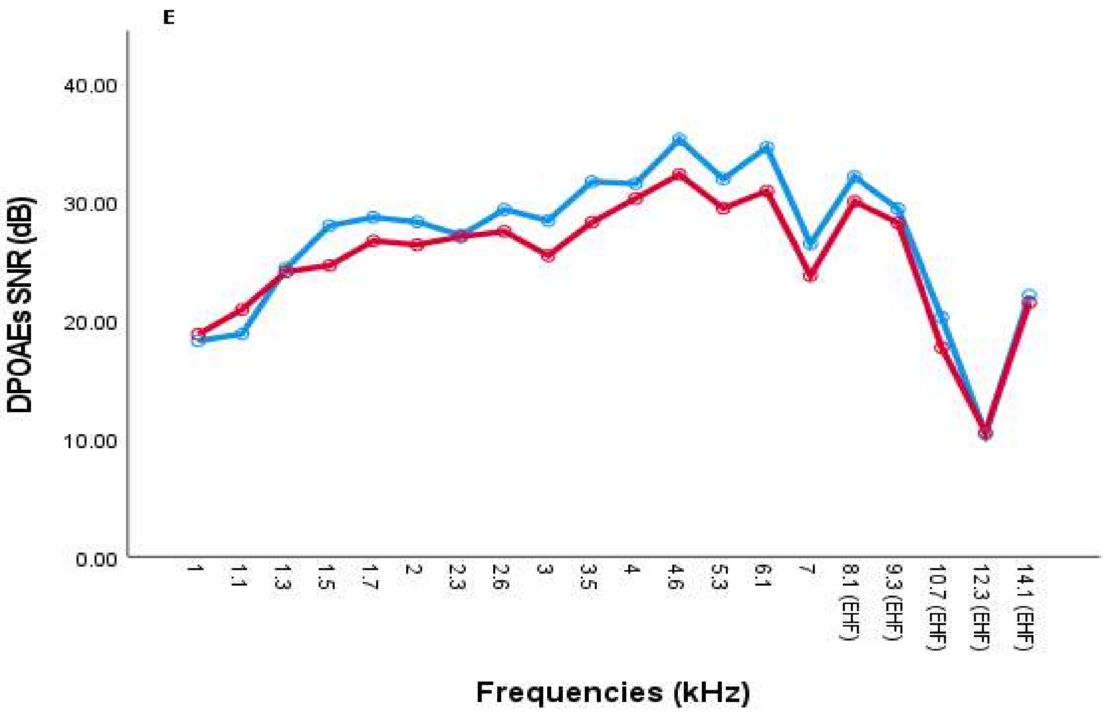


Figure 3.9: Mean values across the 29 subjects in the high-and low-noise exposure groups of the main hearing measures plotted against frequency. Red line: High NESI group; Blue line: Low NESI group. Panel (A): HTL vs. audiometric frequency. Panel (B and C) TEOAE signal amplitude and SNR respectively from the TEOAE-HPF paradigm vs. ½-octave centre frequency. Panel (D and E) DPOAE signal amplitude and SNR respectively of the DPOAE-70/70 paradigm vs. ½-octave centre frequency.

In summary, for RQ 1b, the null hypothesis that $alpha_2$ is zero (i.e. that there is no interaction between noise-exposure group and frequency range) is accepted for HTLs, and for the signal amplitude and SNRs of EHF-DPOAEs (70/70 paradigm) and TEOAE (HPF paradigm).

3.6.5 Effect of different stimulus paradigms on EHF-OAE

This section addresses RQ 2a and RQ 2b (Section 3.2). In this part of the study, different stimulus conditions were used for EHF-OAEs and were assessed to determine which stimulus condition for EHF-TEOAEs (HPF vs TB [10kHz]) and for EHF-DPOAEs ([65/55] vs [70/70]) evoked higher amplitudes and SNRs for EHF-TEOAEs and EHF-DPOAEs.

When evoking for DPOAEs, both stimulus level and other measurement parameters affect the amplitude and SNR. The three most commonly used stimulus parameters for DPOAEs are the frequency ratio (f2/f1) of 1.22, the 2f1–f2 cubic (result of the 2 pure tones), where the most prominent distortion product response is seen, and the (65/55) stimulus level, which is the level most commonly used in clinical settings. The decision was therefore made to evoke DPOAEs using this stimulus level as one of the levels, which was termed the “lower stimulus level”. As well as the lower stimulus level, a higher stimulus level of (70/70) dB SPL was also used, because in normal hearing subjects, higher DPOAE amplitudes are associated with higher stimulus level for frequencies up to 4 kHz (Nishomo et al., 2001), although this does not necessarily indicate that the DPOAEs show greater sensitivity to cochlear dysfunction (e.g. Gorga et al., 1993). However, it is not clear which primary stimulus levels are likely to be the most sensitive to cochlear dysfunction in the EHF region, where the effect of ME attenuation is likely to reduce the energy reaching the cochlea, compared to lower frequencies, for the same primary levels. Poling et al. (2012) suggested that higher stimulus levels (e.g. >70 dB SPL) may allow greater opportunity to record EHF-DPOAE signals from a larger number of subjects, as SNR would increase with increasing primary level. The DPOAE signal amplitude has been found to increase approximately with input levels of up to 75 dB for CAF-range (Dorn et al., 2001). It is worth mentioning that if the primary levels are too high, there is a danger of generating stimulus artifacts. It worth noting that DPOAE primary levels are expressed in dB SPL measured in the IEC 389-4 ear simulator, rather than in dB HL. Thus, they take no account of the higher RETSPLs in EHF region, which means that, on average, the sensation level of the primaries in the (70/70) paradigm will be considerably lower in the EHF than in the CAF region, due to the factors mentioned in section 2.3.2. This is one reason that the (70/70) paradigm might be more appropriate than the (65/55) paradigm for use in the EHF region.

In analysing EHF-TEOAEs, two stimulus conditions were evaluated. The first is HPF, where the click was high-pass filtered to elicit energy from the EHFs region. The second stimulus condition used was TB (10 kHz); unlike the clicks, the tone burst is not frequently used in clinical settings.

Table 3.15 and Figure 3.10 show the stimulus conditions used for the EHF-OAEs and the measurements with statistically higher findings. The paired t-test was used to compare the difference in means across the sample, and separate analyses were carried out for amplitude (dB SPL) and SNR (dB). Table 3.15 shows that the (70/70) generated DPOAEs were of greater amplitude and SNR ($p<0.05$) than the (65/55), Figure 3.11. As a result of this analysis it was decided that the (70/70) level should be included in the previous analysis (Sections 3.6.3.4 and 3.6.4).

The paired t-test was conducted to analyse the difference in mean between EHF-TEOAE HPF and TB (10 kHz). A separate analysis was conducted for amplitude and SNR. Results revealed that there were no statistically significant differences between HPF and TB (10 kHz) on either metric, though HPF was higher for both SNR and amplitude, at 1.45 dB and 1.66 dB SPL respectively. Table 3.15 illustrates the difference in mean between the TB (10 KHz) and HPF.

There are two reasons for including only the HPF in the EHF-TEOAE analysis, rather than also including the TB (Section 3.6.3.3 and 3.6.4), the first relates to the statistical analysis described in this section, i.e. there was no statistically significant difference between TB (10 kHz) and HPF, but the HPF average across the frequency band was slightly higher than the TB average. The second reason is that although both methods focus their stimulus energy on the EHF region, TB concentrates on a narrow band in the EHF range, centred at 10 kHz, while the HPF stimulus energy covers a broader region of the EHF range and can therefore evoke more energy in the EHFs than the TB (10 kHz). So, due to broader energy stimulation of the EHF region, as well as reduced subjective loudness (i.e. due to reduced energy in the low-frequency region) the decision was made to use HPF as the main measurement of EHF-TEOAEs in this study and to include it in analyses in future research.

Table 3.15: The mean and SD for the two EHF-DPOAE (averaged across 4 f2-averaged (9.3, 10.7, 12.3, and 14.1 kHz) stimulus levels and the two EHF-TEOAE (averaged across 3 frequency bands (8, 11.3, and 16 kHz) stimulus waveforms, and the p-value for the difference between the stimulus level and stimulus waveforms (N= 58)

EHF-DPOAEs	**Mean/ (SD)**	**Mean difference**
(65/55) SNR (dB)	15.74/ (6.40)	5.37*
(70/70) SNR (dB)	21.11/ (4.57)	
(65/55) Amplitude (dB SPL)	6.59/ (6.52)	5.69*
(70/70) Amplitude (dB SPL)	12.28/ (4.71)	
EHF-TEOAEs	**Mean**	**Mean difference**
HPF SNR (dB)	7.22/ (5.73)	1.45
TB (10 kHz) SNR (dB)	5.77/ (15.10)	
HPF Amplitude (dB SPL)	8.39/ (5.91)	1.66
TB (10 kHz) Amplitude (dB SPL)	6.73/ (14.97)	

Statistically significant at 0.05*

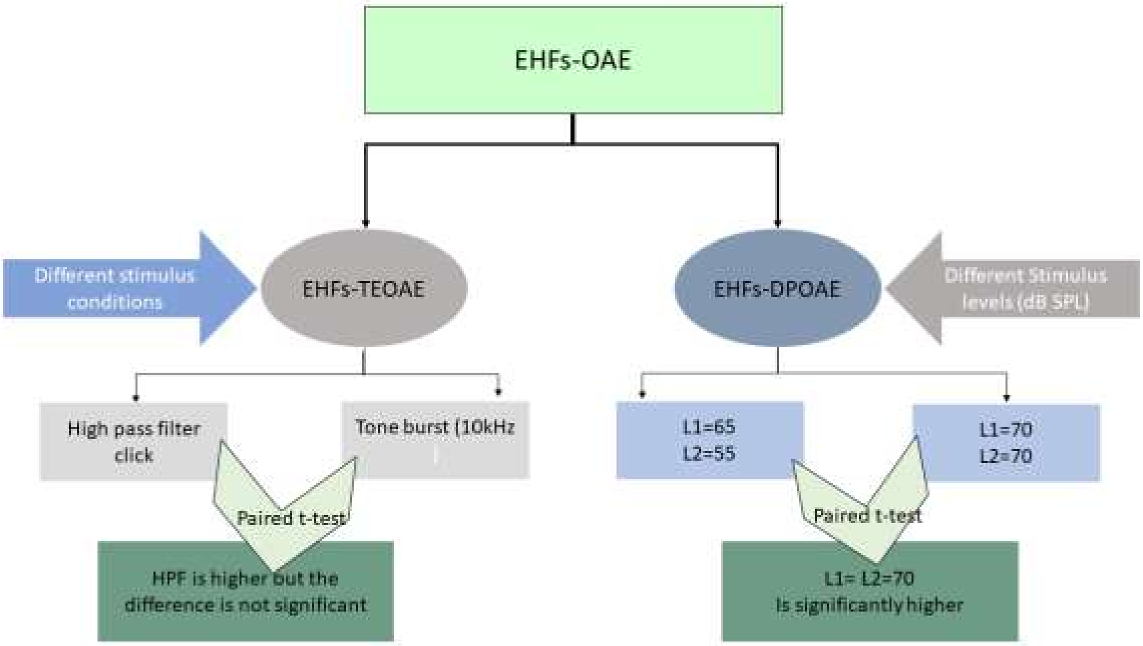
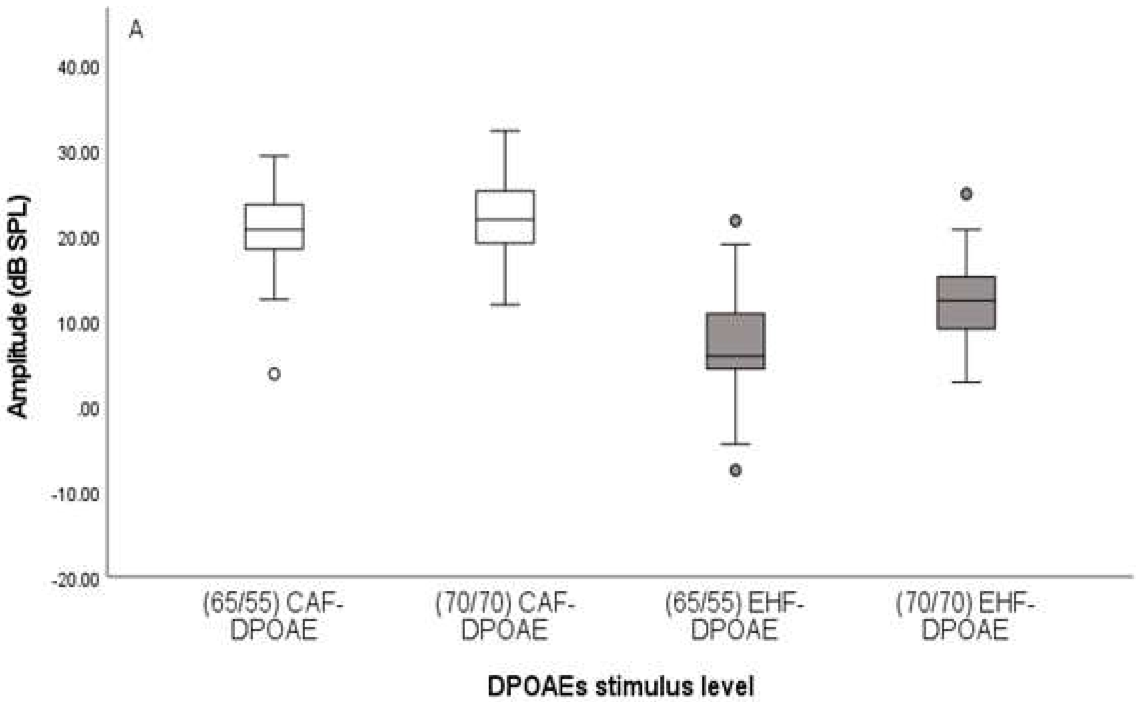
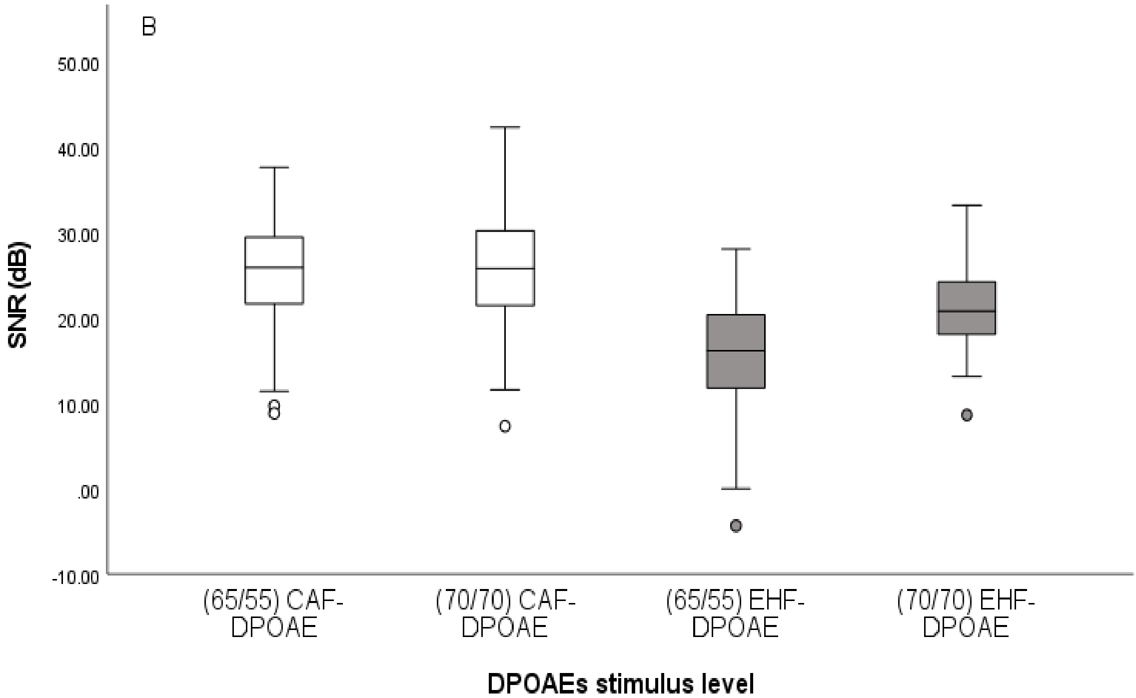


Figure 3.10: Flow chart illustrating stimulus conditions used for EHF-OAEs, and which one was statistically between means across the sample (n=58). The right column shows the low (65/55) and high (70/70) stimulus levels used for EHF-DPOAEs. The left column shows the stimulus waveforms used for evoking EHF-TEOAEs. HPF and 70/70 were selected for inclusion in the main experiment analysis.


A
Amplitude (dB SPL)
40.00
30.00
20.00
10.00
.00
-10.00
-20.00
(65/55) CAF-DPOAE
(70/70) CAF-DPOAE
(65/55) EHF-DPOAE
(70/70) EHF-DPOAE
DPOAEs stimulus level


B
SNR (dB)
50.00
40.00
30.00
20.00
10.00
.00
-10.00
(65/55) CAF-DPOAE
(70/70) CAF-DPOAE
(65/55) EHF-DPOAE
(70/70) EHF-DPOAE
DPOAEs stimulus level

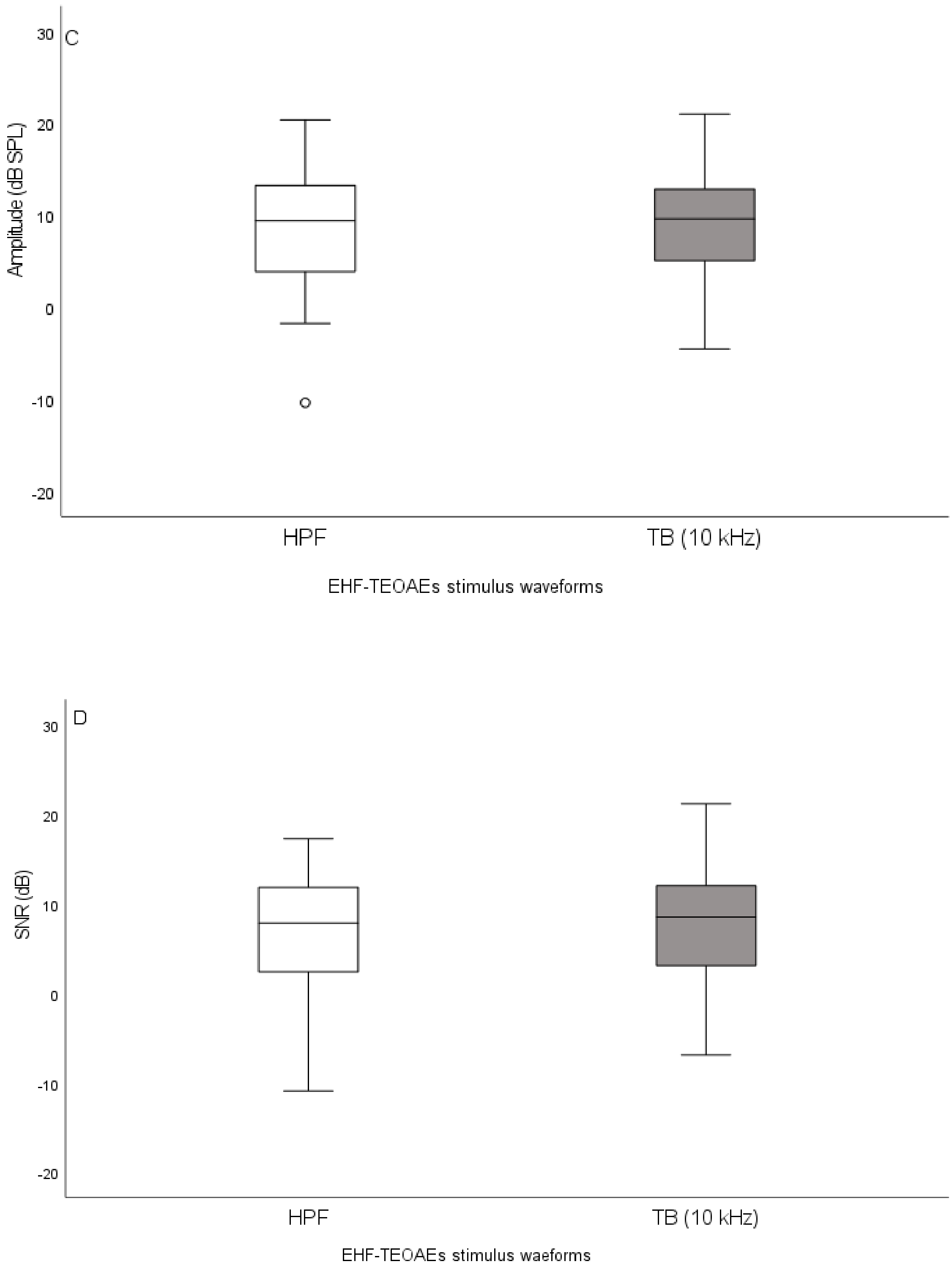


Figure 3.11: Box-and whisker plots for OAE mean outcomes averaged across the sample. Circles indicate minor outliers. Panel (A) shows DPOAE amplitude: grey boxplots indicate EHF-DPOAE amplitude and white boxplots CAF-DPOAE amplitude, which are used for descriptive purposes only. Panel (B) shows the SNR of DPOAEs, corresponding to the measurements described for (A). Panel (C) shows EHF-TEOAE amplitudes: white boxplots show HPF click, and grey show TB 10 kHz amplitudes. Panel (D) shows EHF-TEOAE SNRs corresponding to the measurements described for (C).

3.6.6 Correlations between EHF-OAE measurements

Correlational analyses were conducted to address part of RQ 3 (Section 3.2), where the Pearson correlation coefficients were calculated between EHF-HTLs and the various OAE measurements, and also between every OAE measurement and every other OAE measurement. The results are presented in Table 3.16, where statistical significance has been calculated without correction for multiple tests. As expected, nearly every measurement is significantly correlated with every other measurement. The EHF-HTLs are more strongly correlated with the (65/55) EHF-DPOAEs than the (70/70) EHF-DPOAEs; whether this difference in correlation coefficient is statistically significant is tested in the next section. Pearson's correlation showed that EHF-TEOAEs are positively significantly correlated with EHF-DPOAEs.

Table 3.16: The bivariate correlation between EHF-DPOAEs at 70/70 and 65/55, and EHF-TEOAEs (TB 10 kHz and HPF) with EHF-HTL, N = 58.

Pearson Correlation	EHF-HTL	(70/70) DPOAE amplitude	(65/55) DPOAE amplitude	(70/70) DPOAE SNR	(65/55) DPOAE SNR	HPF TEOAE amplitude	TB (10 kHz) TEOAE amplitude	HPF TEOAE SNR	TB (10 kHz) TEOAE SNR
(70/70) DPOAE amplitude	-0.34**	1							
(65/55) DPOAE amplitude	-0.53**	0.85**	1						
(70/70) DPOAE SNR	-0.17	0.69**	0.57**	1					
(65/55) DPOAE SNR	-0.51**	0.69**	0.87**	0.74**	1				
HPF TEOAE amplitude	-0.47**	0.61**	0.71**	0.38**	0.62**	1			
TB (10 kHz) TEOAE amplitude	-0.52**	0.39**	0.62**	0.21	0.54**	0.70**	1		
HPF TEOAE SNR	-0.43**	0.53**	0.64**	0.27*	0.54**	0.95**	0.69**	1	
TB (10 kHz) TEOAE SNR	-0.51**	0.36**	0.59**	0.18	0.52**	0.69**	0.98**	0.69**	1

Correlation is statistically significant at 0.01**, statistically significant at 0.05*

3.6.6.1 Comparing correlations between EHF-OAE and HTL measurements

This section addresses RQ 2a and 2b and RQ 3 (Section 3.2). According to the correlations reported in the previous section, a further analysis was made to compare the R-values. Table 3.17 compares the R values from Table 3.16, and tests the difference for significance (Meng et al., 1992), to find out whether the coefficients of EHF-TEOAEs (HPF and TB of amplitude and SNR) are significantly different from each other. Similarly, the difference between the coefficients of EHF at both 70/70 and 65/55 were noted, for amplitude and SNR separately. Table 3.17 illustrate the Pearson's correlation coefficient and the significant differences between the correlations. As shown in Table 3.17, the (65/55) EHF-DPOAEs correlate more strongly with EHF-HTL than the (70/70) EHF-DPOAEs, and the differences in R-values are statistically significant.

Table 3.17: Pearson's correlation of EHF-HTL and EHF-OAE measurements, as well as the comparison between the R-value of the EHF-OAEs. Columns 1 and 2 values are taken from Table 3.16 above.

R-values	R-values	Difference in R-values
DPOAE (70/70) amplitude vs. HTL -0.34**	DPOAEs (65/55) amplitude vs. HTL -0.53**	0.19**
DPOAE (70/70) SNR vs. HTL -0.17	DPOAEs (65/55) SNR vs. HTL -0.51**	0.34**
TEOAE HPF amplitude vs. HTL -0.47**	TEOAEs TB amplitude vs. HTL -0.52**	0.05
TEOAE HPF SNR vs. HTL -0.43**	TEOAEs TB SNR vs. HTL -0.51**	0.08

Statistically significant at 0.01**
Statistically significant at 0.05*

3.6.6.2 Comparing correlations between CAF and EHF measurements

The question of how strongly the CAF and EHF measurements correlate with each other (RQ 3) were tested with Pearson's correlation. This gives an indication of the extent to which EHF-measurements can be predicted from CAF measurements, and hence may be redundant, at least in this study population. Table 3.18 shows Pearson's correlation between the EHF-HTL and both CAF and EHF-OAEs. As expected, there were significantly negative correlations between EHF-HTL and EHF-TEOAE amplitude and SNR, and with EHF-DPOAE amplitude, but no significant correlation was found between EHF-HTL and EHF-DPOAE (70/70) SNR. It worth mentioning that some of the data from Table 3.16 have been repeated in 3.18 and 3.19 to aid comparison.

Table 3.18: The correlation between the HTL and OAE measurements, N = 58. Values in italic font are repeated from previous tables.

Pearson Correlation between CAF-HTL		Pearson Correlation between EHF-HTL	
EHF-HTL (dB HL)	0.47**	CAF-DPOAE (70/70) amplitude (dB SPL)	-0.26*
CAF-DPOAE (70/70) amplitude (dB SPL)	-0.36**	CAF-DPOAE (70/70) SNR (dB)	-0.2
CAF- DPOAE (70/70) SNR (dB)	- 0.33*	EHF-DPOAE (70/70) (amplitude dB SPL)	*-0.34***
EHF-DPOAE (70/70) amplitude (dB SPL)	-0.31*	EHF-DPOAE (70/70) SNR (dB)	*-0.17*
EHF-DPOAE (70/70) SNR (dB)	-0.34**	CAF-DPOAE (65/55) amplitude (dB SPL)	-0.37**
CAF-DPOAE (65/55) amplitude (dB SPL)	-0.48**	CAF- DPOAE (65/55) SNR (dB)	-0.22
CAF- DPOAE (65/55) SNR (dB)	-0.30*	EHF-DPOAE (65/55) amplitude (dB SPL)	*-0.53***
EHF-DPOAE (65/55) amplitude (dB SPL)	-0.42**	EHF-DPOAE (65/55) SNR (dB)	*-0.51***
EHF-DPOAE (65/55) SNR (dB)	-0.49**	CAF-TEOAE amplitude (dB SPL)	-0.29*
CAF-TEOAE amplitude (dB SPL)	-0.31*	CAF-TEOAE SNR (dB)	-0.22
CAF-TEOAE SNR (dB)	- 0.27*	EHF-TEOAE HPF amplitude (dB SPL)	*-0.47***
EHF-TEOAE HPF amplitude (dB SPL)	- 0.25	EHF-TEOAE HPF SNR (dB)	*-0.43***
EHF-TEOAE HPF SNR (dB)	- 0.22		

** Correlation is significant at 0.01
* Correlation is significant at 0.05

Table 3.19: The correlation between both DPOAEs and TEOAEs, of CAF and EHF measurements, N = 58. Values in italic font are repeated from previous tables.

Pearson Correlation	CAF-DPOAE (70/70) amplitude (dB SPL)	CAF-DPOAE (70/70) SNR (dB)	CAF-TEOAE amplitude (dB SPL)	CAF-TEOAE SNR (dB)	EHF-DPOAE (70/70) amplitude (dB SPL)	EHF-DPOAE (70/70) SNR (dB)	EHF-TEOAE HPF amplitude (dB SPL)	EHF-TEOAE HPF SNR (dB)
EHF-DPOAE (70/70) amplitude (dB SPL)	0.50**	0.31*	0.41**	0.39**	1			
EHF-DPOAE (70/70) SNR (dB)	0.33*	0.30*	0.31*	0.24	*0.69***	1		
EHF-TEOAE HPF amplitude (dB SPL)	0.39**	0.19	0.38**	0.26*	*0.61***	*0.38***	1	
EHF-TEOAE HPF SNR (dB)	0.37**	0.21	0.35**	0.25	*0.53***	*0.27**	*0.95***	1

** Correlation is significant at 0.01
* Correlation is significant at 0.05

3.6.7 Prediction of EHF-HTL from EHF-OAE measurements

One of the research questions asks how well OAEs can predict EHF-HTLs (RQ 3, Section 3.2), and since the outcome of both SNR and amplitude are looked at and included in the analysis, this study aims to compare the correlation of SNR (DPOAEs vs TEOAEs) with HTL, and amplitude (DPOAEs vs TEOAEs) with HTL, to determine if there are significant differences between them. The R-values of amplitude and SNR EHF-OAEs in relation to EHF-HTL were compared to find whether there was a statistically significantly difference between EHF-TEOAE and EHF-DPOAE amplitude and SNR (Meng et al., 1992), as shown in Table 3.20. There were no statistically significance in the difference between R-value, meaning that both SNR and amplitude predicte EHF-HTL at similar level. This table confirms the findings above, which suggest a negative trend in the relationship between HTL and OAEs at EHFs, which was expected, as a similar trend was seen in the CAF range Table 3.16 showed that EHF-DPOAE (65/55) is more strongly correlated with EHF-HTLs than is EHF-DPOAE (70/70) might indicate that the low stimulus level can be a predictor of EHF-HTL. The table also shows that EHF-DPOAE (70/70) amplitude was significantly correlated with EHF-HTL, while the SNR was not significant.

Table 3.20: The correlation of EHF-OAEs and EHF-HTL, and the comparison between statistically significant values of EHF-OAE SNR and amplitude. Selected values taken from Tables 3.16 and 3.17 above.

R-value	R-value	R-value	Difference of columns 2 and 3 R-values
(70/70) amplitude Vs. HPF amplitude 0.61**	(70/70) amplitude vs. HTL -0.34**	HPF amplitude vs. HTL -0.47**	0.13
(70/70) SNR vs HPF SNR 0.27*	(70/70) SNR vs. HTL -0.17	HPF SNR vs. HTL -0.43**	0.26
(65/55) amplitude Vs. HPF amplitude 0.71**	(65/55) amplitude vs. HTL -0.53**	HPF amplitude vs. HTL -0.47**	-0.06
(65/55) SNR vs HPF SNR 0.54**	(65/55) SNR vs. HTL -0.51**	HPF SNR vs. HTL -0.43**	-0.08

** Correlation is significant at 0.01
* Correlation is significant at 0.05

In summary, of correlation addressed in RQ 3 The EHF-HTLs were negatively correlated with the EHF-OAEs. Although the correlation was stronger with EHF-TEOAEs and EHF-DPOAEs (65/55) than with EHF-DPOAEs (70/70). This difference in correlation coefficient was tested by comparing the R-values that found to be statistically significant. Pearson's correlation showed that EHF-TEOAEs are positively significantly correlated with EHF-DPOAEs.

3.6.8 Further exploratory analysis

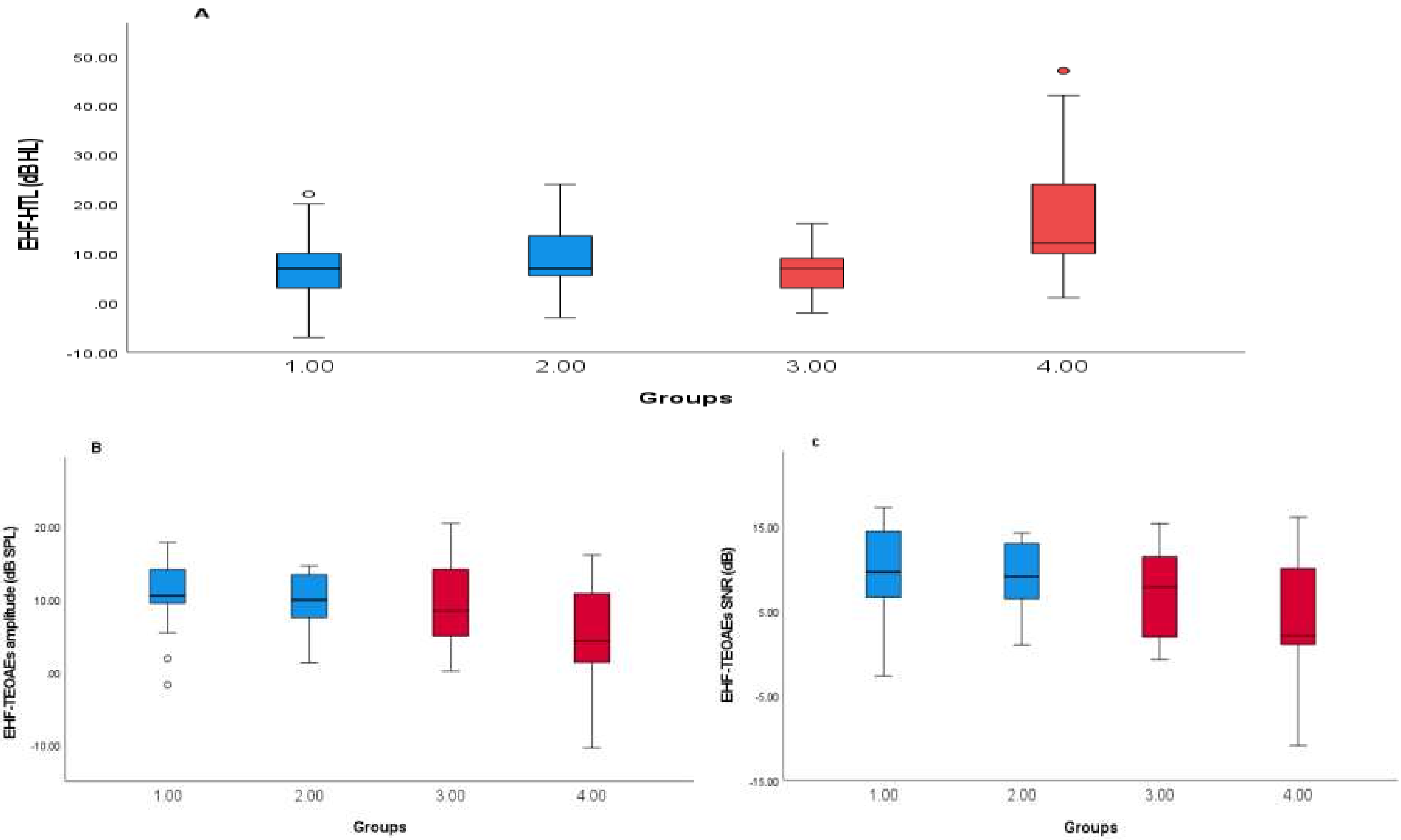
A further exploratory (i.e. unplanned) statistical analysis was conducted that repeated the split-plot ANOVA but split the sample into four groups instead of two, so instead of assigning participants based on the median 50 percentile of the NESI score, the participants were allocated based on the interquartile range (IQRs) of the NESI score. In the exploratory analysis, the subjects were assigned to four groups (Gp) (i.e. Gp 1 [n=14], Gp 2 [n=15], Gp 3 [n=15], and Gp 4 [n=14]) the first two were from the lower- NESI group and the latter two were from the higher- NESI group. The rationale for this further analysis was that in the 2-group analysis, the higher- NESI group had a wide range of NESI scores, and a high proportion of subjects with relatively low NESI scores can dilute the effect of higher NESI scores. Using four groups can overcome the low NESI sores in the high- NESI group (Table 3.21). Box plots in Figure 3.12 show the differences between the four groups.

Exploratory analysis was conducted that in this case, meaning that this analysis was not planned (a priori) from the beginning of the study but emerged after reporting the results of the planned analysis (the reason behind the application of exploratory analysis will be mentioned later in the section). This means that the results are taken with caution and are not reported, as there is a danger of HARKing (or p-hacking – i.e. trying out lots of analyses and picking the one with $p<0.05$). The exploratory study is useful as an indicator for future work, rather than as a rigorous testing of an a priori hypothesis.

Table 3.21: Subject allocations into four groups based on IQR, showing NESI scores

Groups	Number of subjects	NESI score Mean /(SD)	NESI score Median	Group classification
Gp 1	14	0.26/ (0.30)	0.13	Low- NESI
Gp 2	15	4.30/ (1.57)	4.03	Low- NESI
Gp 3	15	11.87/ (2.45)	12.46	High- NESI
Gp 4	14	39.68/ (20.24)	36.31	High- NESI

The split plot NOVA showed statistically significant interaction term between NESI group and frequency range of CAF-HTLs and EHF-HTLs ($p < 0.05$). In addition, statistically significant interaction term between NESI group and frequency range for EHF-TEOAEs (amplitude and SNR) and EHF-DPOAEs amplitude ($p < 0.05$). All groups were compared in relation to Gp 4, the high noise exposure group. It should be noted that these were unplanned statistical tests, and therefore the results should be treated with more caution than tests of a priori hypotheses.


A
EHF-HTL (dB HL)
50.00
40.00
30.00
20.00
10.00
.00
-10.00
1.00
2.00
3.00
4.00
Groups
B
EHF-TEOAEs amplitude (dB SPL)
20.00
10.00
.00
-10.00
1.00
2.00
3.00
4.00
Groups
C
EHF-TEOAEs SNR (dB)
15.00
5.00
-5.00
-15.00
1.00
2.00
3.00
4.00
Groups

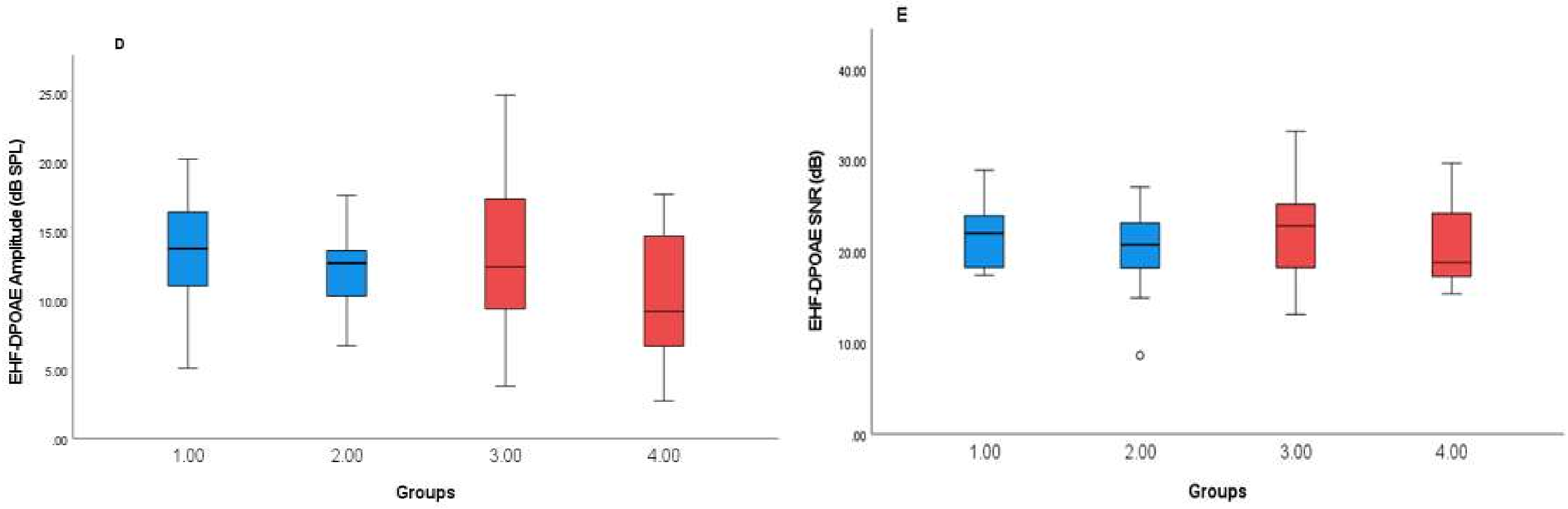


Figure 3.12: Box-and-whisker plots for the outcome of the four groups. The blue boxes are the two low NESI groups, and the red boxes are the two high NESI groups. Circles indicate minor outliers. (A) EHF-HTL in dB HL. (B) EHF-TEOAE amplitude (HPF) in dB SPL. (C) EHF-TEOAE SNR (HPF) in dB. (D) EHF-DPOAE (70/70) amplitude in dB SPL. (E) EHF-DPOAE SNR (70/70) in dB.

3.7 Discussion

3.7.1 Effect of NESI score on CAF-HTLS and EHF HTL

This study aimed to assess the effect of noise exposure on hearing measurements by answering the following questions: what effect does noise exposure have on hearing measurement, and is the effect greater at EHFs than at CAFs? Both CAF and EHF ranges were evaluated using PTA, DPOAEs, and TEOAEs. The outcome data that were averaged across CAF and EHF were analysed with LMM and split-plot ANOVA.

The effect of noise exposure on HTL has been reported in the literature (Wang et al., 2008; Mehrpharvar et al., 2011; Sulaiman et al., 2014; Kumar et al., 2017). The current LMM analysis reported likely similar effects of noise exposure on HTL, as findings show that the 7-average-frequency CAF-HTL increases with increasing NESI score. However, these effects were not seen in the planned split-plot ANOVA analysis, thus weakening confidence in the results of the LMM. One possible reason for this is that the designed sample population had to have CAF-HTLs of ≤ 20 dB HL (i.e for both high and low- NESI groups), so this placed a limit on the degree of any HL at CAF (but not on EHF).

Furthermore, 18 kHz was analysed separately using the Mann-Whitney test, and no statistically significant difference was reported between groups. There are several possible explanations for this, relating to the ISVR noise exposure limit followed in this study, whereby the stimulus tone level was limited to no more than 105 dB SPL, or 50 dB HL. For the ISVR noise exposure limits, the stimulus tone level was limited to no more than 50 dB HL, or 105 dB SPL (whichever was the lower). For 18 and 16 kHz, when the threshold was beyond this exposure limit, it was assigned as “no response”. These limits are based on the ISVR requirement to ensure that the LAeq 8hr does not exceed 76 dBA, as specified in ISVR Technical Memo No. 808 (Griffin et al., 1996).

In the current study, 11 subjects were reported to have no response as they had reached this limit, and “no response”, coded as 110 dB SPL, was set for these subjects in order to make a comparison. However, the actual HTL for these subjects may have been higher, but, due to the limit, this would not have been recorded, unlike for Korres et al. (2008) who did not have such a restricted limit of allowable measurements for 18 kHz (reported mean HTL = 74.4 dB HL).

The current results of LMM analysis also indicated that the 5-frequency average EHF-HTLs correlated with noise exposure more strongly than CAF-HTLs. At least some studies have reported that EHF-HTLs are greater than CAF-HTLs in people exposed to noise (Ahmed et al., 2001;

Mehrpharvar et al., 2011). Therefore, in the current study it was expected that noise exposure might impact HTL at EHFs, as there is a positive correlation between them, with higher NESI scores corresponding to greater EHF-HTL. The present study findings from the LMM analysis were qualitatively (i.e. in terms of direction of effect rather than absolute numbers) similar to previous studies, in which 5-frequency average EHF-HTLs were more affected by NESI score than were the 7-frequency average CAF-HTL. For instance, the LMM analysis in the current study suggested that when there is an increase of one unit in NESI score, there was an increase of 0.25 dB HL in 5 frequency-average EHF-HTL, with a 7-frequency CAF average increase of 0.04 dB HL. This agrees with the hypothesis proposed in the current study, that noise exposure affects HTL to a greater degree with EHF-HTLs than CAF-HTLs. Mehrpharvar et al. (2011) reported that higher EHF-HTL is associated with increased noise exposure. An association between noise exposure and EHF-HTL was reported, even for young adults with CAF-HTL ≤ 25 dB HTL (Sulaiman et al., 2014; Liberman et al., 2016; Prendergast et al., 2017).

Ahmed et al. (2001) reported significantly higher hearing thresholds at EHFs for participants who were exposed to noise than those not exposed, and Liberman et al. (2016) reported higher HTL at EHFs, growing to ~20 dB HL at 16 kHz between groups. The current study and above-mentioned studies agree with the hypothesis that HTL is impacted by noise-exposure, and EHF-HTLs may be more useful in the early detection of NIPTS, since in this study, the mean of HTLs suggests that the noise-exposed population is more affected in the EHF-range than the CAF-range; however, looking only at the size of the change in mean is not the whole story, and inter-subject variability is also important in determining how well noise exposure is predicted by HTLs. This finding is not surprising, as it may suggest that a cochlea that is somewhat damaged at CAF range tends to be also damaged at EHF range. This would mean that any measure of hearing in the CAF range is correlated with the same measure in the EHF range (CAF HTLs vs. EHF HTLs, etc). For example, noise exposure will affect both regions, as will smoking, diet, and genetics, so these correlations are all expected to some extent.

Despite consistency in the findings of the current LMM analysis with some of the previous research, the LMM was at the same time inconsistent with other studies that found the effect of noise exposure no different at the EHF-HTL than the CAF-HTL. Such inconsistency can be seen with previous studies that reported no statistically significant association between noise exposure and EHF-HTL (Silvestre et al., 2016; Wei et al, 2017). One explanation for the inconsistent results may be that some of the studies considered only one activity of noise exposure (e.g. PLD use) without accounting for other noise sources activities. Another possible reason for the lack of correlation between noise exposure and EHF-HTL might be the difficulty of accurately estimating lifetime noise exposure, as the estimates are largely dependent on self-reporting (i.e. estimated information on the events of noise exposure, duration of noise exposure, and level of exposure).

An approximate quantitative analysis can also be conducted to compare the changes in CAF-HTLs in the current study with predictions of NIPTS using the formula in ISO 1999. It worth mentioning that ISO 1999 (ISO, 1999; 2013) covers NIPTS only up to 6 kHz, and therefore due to the limitation in EHF data the NIPTS is only estimated for the CAF range. The estimate was possible because NIPTSs are related to the level of noise exposure in dB SPL and duration of exposure and the NESI score also separately estimates activity SPLs and duration. For example, a NESI score of 10 units would be obtained for 10 years of exposure to 90 dBA. ISO 1999 then predicts median NIPTS of 0, 2, 8, 11, and 7 dB at 1, 2, 3, 4, and 6 kHz respectively (ISO, 1999; 2013). So a 5-frequency average of the median NIPTS (1, 2, 3, 4, and 6 kHz) would be 5.6 dB for a NESI score of 10 (see Appendix C). The estimation of NIPTS for our data is as follows. Since the mean of the NESI score is 13.8 units and the regression coefficient of CAF-HTL due to noise exposure is 0.04 dB HL, for 10 years of exposure the CAF-HTL could shift by a magnitude of 5.52 dB HL. The current NIPTS of 5.52 dB (Appendix C) at the CAF range is lower than that predicted, i.e. with 1 unit of NESI score there is an increase of 0.056 dB HL, and 7.72 dB HL NIPTS in CAF-HTL over 10 years (Appendix C). Note that this calculation is just a very rough comparison of the order of magnitude of the HTL elevation that was measured, compared to the NIPTS predicted from ISO 1999 for a similar predicted degree of noise exposure. This comparison is based on a number of simplifications in the relationship between the ISO-predicted NIPTS (ISO-NIPTS) and the NESI score. In reality, the ISO-NIPTS is not simply linearly related to the NESI score, but rather shows a non-linear relationship between personal daily exposure level in dBA and exposure duration. In addition, the current study only include participants who with normal CAF-HTLs, thereby limiting the degree of any NIHL for CAF-HTLs.

Estimating the lifetime noise exposure was conducted in order to compare the degree of noise exposure and NIPTS in the current study to previous studies (Table 3.15). It will allow a rough comparsion of the NESI score degree in the current study with that of previous studies. Unfortunately, these estimates cannot be applicable to all studies as there is lack of information about the noise exposure. For example, in some of the occupational noise exposure studies, participants were assigned to low or high NESI groups based on their occupation (i.e. if they worked in a noise-exposed environment, they were assigned to a noise-exposed group and if not, they were assigned to a non-noise-exposed group) and not much information on other noise exposure events were taken into account. Another reason is that some studies account for only one source of noise exposure, such as Sulaiman et al. (2014) who studied PLD use as the only source of noise exposure.

Table 3.22 compares the current study NIPTS with previous studies. There are variations between NIPTS in the current study and other studies. The NIPTS of the current study was lower than that reported by Ahmed et al. (2001) and Mehrprvar et al. (2011); these authors did not limit CAF-HTL as in this current study i.e. inclusion of CAF-HTL ≤ 20 dB HL. Table 3.22 also shows lower NIPTS for the current study than what was expected based on the median of the current NESI score. This variation has also been noticed for Prendergast et al. (2018), who used the NESI score to quantify lifetime noise exposure. One possible reason is that the the NESI questionnaire is a self-assesment, in which true noise exposure may have been over-estimated (at least in the current sample), leading to erroneous measurements of lifetime noise exposure. Another reason might be that the NESI score is affected by a number of outliers, which could explain why few effects of noise exposure were observed. These comparisons can be difficult to make accurately, because of the many differences between studies in terms of age, lifestyle, and the spectral and temporal nature of noise exposure.

Table 3.22: Summary of study of changes in CAF-HTL

Studies	Estimated Exposure		Estimated NESI units in exposed group	Measured CAF HTL (dB HL) Exposed/non-exposed	Measured NIPTS at CAF frequencies (dB HL) (exposed – unexposed)
	L_{Aeq} SPLs (dBA)	Duration of exposure (years)			
Current study	N/A	N/A	13.8[b]	From regression	5.52 [b]
Somma et al., 2008	85	≥ 1 [a]	N/A	15/10.5	15 – 10.5 = 4.5
Ahmed et al., 2001	>85	N/A	N/A	24.2/15.7	24.2–15.7= 8.5
Mehrparvar et al., 2011	89.07	10.72	N/A	16.17/9.14	16.17–9.14= 7
Prendergast et al., 2018	N/A	N/A	31.6 [c]	3.9/1.44	3.9–1.44=2.5
Wang et al., 2022	94.8	8.9	N/A	17/15.4	17–15.4= 1.6

Notes: the noise-exposed workers had been employed for at least 1 year before enrolment.
The current study NESI score mean and for 10 years of exposure, shows the CAF-HTL shift of a magnitude of 5.52 dB HL [b].
This study estimated noise exposure using NESI score, with 31.6 as the noise-exposed group mean, while 0.10 is the low-exposure group NESI mean [c].

Two questions were addressed in this analysis. First, is there any effect of NESI score on measurements of hearing status, and second, was the effect of NESI score greater at EHFs than at CAFs?

When assessed using the Split-ANOVA, neither of these effects was statistically significant. When comparing the findings to other studies, an important consideration is the degree of noise exposure in the groups. In the present study, the exposure groups were defined using the median NESI score of 7.69 units as the cut off. This equates to approximately 7 years of noise exposure to 90 dBA (or 10 year at 88.5 dBA). One reason for the lack of any significant effect may be that the exposure in the “high-NESI” group included a proportion of participants with relatively minor noise exposure. To explore the discrepancy between the LMM and split-plot ANOVA results further, an exploratory analysis was conducted with the subjects assigned to groups based on IQRs of NESI score instead of median based alignment to groups (Section 3.7.1.1), that reported a significant main effect of NESI score in the high- NESI group with highest NESI (Gp 4), but with the caveat that this was not a planned analysis.

It worth mentioning that the study design of the previously mentioned studies, along with this section of the current project, is a cross-sectional design, so there is a chance that results are affected by confounding variables (e.g. a tendency towards high recreational noise exposure may be correlated with other lifestyle choices relating to smoking, diet, exercise, and sleep).

It also worth noting that looking only at the mean differences between groups or the LMM coefficient does not tell the full story about which frequency range is the most clinically useful; this would depend on the application – e.g. whether regular measurements are made for monitoring purposes, to detect changes from a baseline, or whether a clinician is making an assessment based on a single measurement. The intra- and inter-subject variability becomes important in these cases.

3.7.1.1 **Discussion of Exploratory Analysis Group 4**

In the 2-group analysis, the high-NESI group still had a high proportion of participants with relatively low NESI scores, making a large proportion of the participants close to the cut-off point criteria for the low and high NESI group. This can dilute the effect of the NESI score. To address this issue, quartiles group classification was introduced, with two low NESI groups and two high NESI groups. This led to a high proportion of participants with elevated NESI scores in the highest NESI group, which can assess the effect of noise exposure more efficiently. The split-plot ANOVA showed that Group 4, which was the highest high- NESI group, had statistically greater HTL at EHFs than the other groups. EHF-TEOAEs were statistically significantly different between the low-

NESI and high-NESI groups, as the two high NESI groups were statistically significantly greater than the two low-NESI groups. One explanation as to why there were differences between the IQR-based groups and not in the 50%-based, is that with only two groups, there may have been high-NESI individuals with low NESI score, and most of the values were concentrated close to the cut-off point of 7.69 NESI. In contrast, having four groups would increase the value of NESI score in the highest high-NESI group (Gp4).

3.7.2 Effect of lifetime noise exposure on EHF DPOAEs and EHF TEOAEs

This section discusses the LMM results of (70/70) and (65/55) DPOAEs and HPF-TEOAEs, to assess the results of RQ 1a (Section 3.2). While it has long been known that CAF-OAEs have lower amplitude as a result of excessive noise exposure, far fewer studies have examined the effect of noise on EHF-OAEs. Sulaiman et al. (2014) reported that CAF-TEOAEs, CAF-DPOAEs, and EHF-HTL all detected signs of the early stages of hearing damage better than CAF-PTA when noise exposed. Using EHF-OAEs to measure cochlear function could be beneficial in detecting signs of cochlear changes. In the current study, a hypothesis was tested regarding the susceptibility of EHF-TEOAEs and EHF-DPOAEs to noise exposure. It was hypothesised that EHF-DPOAE and EHF-TEOAE amplitude and SNR are more affected by NESI score than those in the CAF range.

In the current LMM results CAF and EHF-DPOAE (65/55) amplitude and SNR were found to be statistically significantly predicted by NESI score, with negative regression coefficients, no statistically significant additional effect on EHF-DPOAEs above CAF. For CAF- and EHF-DPOAE (70/70), the signal amplitude but not the SNR was found to be statistically significantly predicted by NESI score. The fact that for DPOAE (70/70), the signal amplitude showed a significant effect but the SNR did not might be related to signal amplitude giving a direct estimate of the OAE signal generated by the cochlea, while the SNR estimates the ratio of the OAE signal to the measurement noise, and so depends not just on the cochlea, but also on physiological which can have several different causes such as movement artefacts, as well as breathing and heart beat. In addition, no statistically significant additional effect of NESI on amplitude and SNR of EHF-DPOAEs using (70/70) and (65/55) over and above the effect on CAF-DPOAEs. This does not mean that the EHF was not affected by NESI; only that there was no additional effect of NESI score on EHF-DPOAEs compared to the overall change in both CAF and EHF.

This finding was consistent with Sulaiman et al. (2014), who reported lower DPOAE amplitude in PLD users. Exposure to noise impacts the OHCs, and can be directly assessed from DPOAEs. The effect of noise can be associated with a reduction in the amplitude and SNR of DPOAEs. The previous study did not assess the EHF-DPOAEs.

Narniah et al. (2017) reported in their experimental study that EHF-DPOAE (up to 12 kHz) amplitude was significantly reduced after noise exposure. But due to the nature of the study, the reduction of amplitude could have been due to TTS, as baseline measurement of DPOAEs was conducted followed by a retest of DPOAEs post 2 hrs of PLD usage, with an average noise level of 98.29 dB(SPL). As mentioned earlier, changes may have been due to TTS rather than PTS and there was no follow up to check for subject recovery. Their findings show that only EHF-DPOAEs increased in association to noise exposure, while the current study indicates that EHFs were affected to the same extent as CAFs.

A possible explanation for why, in the current LMM analysis, no statistically significant interaction term between NESI score and frequency range between CAF and EHF-DPOAEs, is that the standing wave in the ear canal tends to emphasise or de-emphasise the EHF component depending on the individual’s ear canal. This leads to increased inter-subject variability. Another reason relates to the ME transmission function that does not adequately transmit the EHF signal from and to the cochlea. This can lead to insufficient recording of the EHF-DPOAE amplitude, and therefore, no association would be reported.

Not seeing a similar effect of noise exposure on EHF-OAEs as was found with EHF-HTL. This might be due to the reasons that the ear canal resonant frequency characteristic, which in the EHF-OAEs does not just affect the inward signal as HTL, impacted by the outward signal (Charaziak and Shera, 2017). Furthermore, the reverse transmission of sound from the cochlea to the ear also reduces rapidly with high frequencies, which affects OAEs but not the HTL (Puria, 2003). Thus, this might indicate that measurement of EHF-OAEs is more difficult than the EHF-PTA as the signal is affected by the inward transmission as well as the outward signal recorded in the ear canal.

In the second analysis of the current study (RQ 1b, Section 3.2), split-plot ANOVA found no statistically significant difference between the low and high- NESI groups for both CAF- and EHF-DPOAEs (70/70). This is inconsistent with Dhrruvakumar et al. (2021), who reported a statistically significant difference between EHF DPOAE amplitudes in the group exposed to noise and the group not exposed to noise. In the current ANOVA results, the high- NESI group mean amplitude of EHF-DPOAEs was 11.6 dB SPL, and 12.9 dB SPL for the low- NESI, and a similar trend of difference was observed between groups in the CAF range (low group 22.3 and high 21.7 dB SPL), with greater amplitude for low- NESI group, although the effect was not statistically significant. Similarly, Liberman et al. (2016) reported that there was a difference between groups in EHF-DPOAE amplitude, but that the effect was not statistically significant. In the current ANOVA, not seeing a similar effect of noise exposure on CAF-DPOAEs, as reported by the current LMM, could be because the NESI scores (i.e. self-reported measurements) were over-estimated, at least by the current sample.

It is important to clarify that there was no evidence of the effect of age on the hearing measurements. However, this is likely to be due to the strict inclusion recruitment criteria set in the present study, as only participants 18–35 years were included.

Another aim of the study was to assess the sensitivity of TEOAEs to noise exposure. It was hypothesized that noise exposure affects CAF- and EHF-TEOAEs, with more impact in the EHF-TEOAEs. The current LMM results show that NESI scores statistically significantly affect CAF- and EHF-TEOAE amplitude, with negative regression coefficients. However, the effect of NESI on EHF-TEOAEs was neither higher nor lower than on CAF-TEOAEs, either for amplitude or SNRs. Finding no significant Incremental effect of NESI score on EHF-TEOAE SNRs above that on CAF-TEOAEs may be due to the following reasons that lead to inter-subject variability in the EHF range. The first is that the occurrence of standing waves in the ear canal affect both inward and outward propagation of the OAE, leading to errors in the estimates of the stimulus level and the OAE level (Charaziak and Shera 2017). Second, ME transmission function may impact the inward and outward signal propagation, which can also be a source of greater inter-subject variability. Both these effects will reduce the statistical power of the study for a given sample size.

The split plot ANOVA analysis from CAF- and EHF-TEOAEs showed no statistically significantly main effect of NESI group, with no significant interaction between NESI group and frequency range.

In the current study, the SNR for EHF-TEOAEs was typically lower than for EHF-DPOAEs. For EHF-DPOAEs, most of the subjects had an SNR > 3 dB, while for the EHF-TEOAEs, the SNR was < 3 dB in many cases, even when using the HPF stimulus and DE paradigm. However, SNRs < 3 for a given ear are not clinically useful, and hence EHF-TEOAEs are likely to be less useful clinically than EHF-DPOAEs. Note that the poor SNR (< 3 dB) does not invalidate the use of these results in comparing group differences.

It looks complicated as the findings suggest that noise exposure has a statistically significant effect on HTL for both CAF and EHF, but the statistical significance main effect on EHF region is minimal for the HTL. That means even if there is an observed trend of an increase in EHF-OAE with an increase in NESI score, due to a non-significant finding, the confidence in directing the effect of noise exposure on EHF-OAEs is not very strong. Thus, there is an effect at EHF active of the NESI score, which was statistically significant for the HTL, but was not statistically significant for the EHF-OAE. Although, there was a trend of effect. That is suggesting that, at least for the noise exposure level for the sample included in the study, there is not a large effect. Therefore, further work might be required to investigate the effect of noise exposure in subjects who have greater noise exposure than the current sample.

3.7.3 How strongly do EHF measures correlate with each other?

One of the current chapter aims was to evaluate the correlation between measurements i.e. between different EHF measurements and other EHF and CAF measurements. Two hypotheses were tested: the first proposed that EHF-HTLs were negatively correlated with TEOAE and DPOAE amplitude and SNR for both EHF and CAF ranges, while the second proposed a positive correlation between DPOAEs and TEOAEs for both CAF and EHF. It is well established in the literature that there are significant negative correlations between OAEs and HTL when evaluating the CAF range < 8 kHz (Sistoa et al., 2007; Guida et al., 2012), and that TEOAEs and DPOAEs share some mechanisms relating to their generation and transmission (such as active amplification and ME attenuation), but differ in others (e.g. travelling wave reflections), so they are expected to be only partially correlated.

Guida et al. (2012) reported a negative correlation between CAF-HTL and CAF-DPOAE amplitude; the higher the HTL, the lower the amplitude of the DPOAEs. Similarly, the current study reported a similar correlation between CAF-HTLs and CAF-DPOAEs at (65/55) and (70/70), in both amplitude and SNR. Hall and Lutman (1999) reported the expected trend of a negative correlation between default click CAF-TEOAEs (octave band centred at 3 kHz) and 4 kHz HTLs and a similar trend of correlation was observed with MLS CAF-TEOAEs (octave band centred at 4 kHz) and 4 kHz HTL. There is much less information in the literature on the correlation between EHF-OAEs and EHF-HTL. Similar findings reported in the current study showed that CAF-HTLs were negative significantly correlated with CAF-TEOAE amplitude and SNR. This finding is due to both measurements sharing similar generation sources, both being affected by the active amplification of the OHCs, with the greater amplification leading to lower HTL and higher OAE amplitude.

The current study analysis found a statistically significant negative correlation between the mean frequencies EHF-HTL and the mean frequencies EHF-TEOAE amplitude and SNR. In addition, a negative correlation was found between the mean frequencies EHF-HTL and the mean frequencies EHF DPOAE amplitude. In contrast, the mean frequencies EHF-DPOAE (70/70) SNR did not show significate correlation with EHF-HTL, which was not expected, although it was significant for EHF-DPOAEs (65/55). One explanation for the lack of correlation is that the SNR may be more affected by variability, since it depends on estimated noise as well as the signal, so any effect on SNR may be more hidden by this variability. EHF-DPOAEs (65/55) were also significantly more strongly correlated with EHF-HTLs for both amplitude and SNR than were EHF-DPOAEs (70/70) this is similar to the findings for CAF-DPOAEs (Gorga et al., 2002).

As mentioned above, there was a significant negative correlation between EHF-HTLs and EHF-DPOAEs (65/55), that were not observed for the EHF-DPOAEs (70/70). Moreover, the EHF-DPOAE (65/55) amplitude showed greater correlation with EHF-HTL than EHF-DPOAE (70/70) amplitude, although both were significantly negatively correlated with EHF-HTL. Tai et al. (2022) reported that DPOAE (65/55) amplitudes (i.e. f2 up to 10 kHz) were significantly affected by EHF-HTL. Similar correlation between EHF-HTL and the level of DPOAE amplitude was reported (e.g. Dreisbach et al., 2008), as with higher HTL at EHF, the DPOAEs decrease for frequencies up to 10 kHz, i.e. subjects with lower EHF-HTL had higher DPOAE amplitude compared to those with higher EHF-HTL. This may be because changes in the OHCs did not occur in the CAF region, which is why there was no change in that HTL range, and because OAE and EHF-HTL depend more on the basal location status of the cochlea. The current study also found that EHF-HTL were significantly negatively correlated with CAF-DPOAE amplitude at (65/55) and (70/70).

This correlation between HTL and both TEOAEs and DPOAEs shows that one measurement can be predicted from the other better than chance, but not necessarily accurately enough to be clinically useful in applications where HTLs need to be determined accurately. For example, when the correlation was significant between CAF-HTL and CAF-DPOAE amplitude and the $r = -0.36$, this means that the DPOAEs may predict HTL better than chance. But one should be cautious when dealing with clinical applications that use HTL measurements, such as fitting hearing aids, since predicting from OAEs is not a substitute for accurate HTL measurement. However, OAEs could provide useful complementary information, and better prediction of HTLs might be obtained by combining TEOAE and DPOAE measurements. Recently, Zelle et al. (2017) claimed that CAF-HTLs can be predicted accurately from DPOAEs, but this study used a special paradigm that separates DPOAE components (i.e. non-linear distortion and coherent reflection) using short-pulse stimuli, as well as using the DPOAE growth functions to improve the accuracy of prediction. DPOAEs in combination with optimized stimulus parameters considerably enhances the accuracy of DPOAEs for diagnosing.

Comparison of the correlation of R-values was conducted to assess if there are statistically significant differences between the R-values in the current studies. There were no statistically significant differences between the correlation coefficient R-values of EHF-DPOAE (70/70) and (65/55) amplitudes and EHF-TEOAE HPF amplitudes in their correlation with EHF-HTLs. In addition, no statistically significant differences were found between the R-values of EHF-DPOAE (70/70) and (65/55) SNRs and EHF-TEOAE HPF SNRs in their correlation with EHF-HTLs. This suggests that both EHF-TEOAEs using HPF and EHF-DPOAEs using (65/55) can predict the EHF-HTL quite similarly.

As expected in the current study, there were statistically positive correlations between the frequency-averaged DPOAE amplitude and the band-averaged TEOAE amplitude for both the EHF and CAF ranges. One explanation is that they share a common feature mechanism of cochlear amplifier. In addition, a similar statistically significant positive correlation was found between EHF-DPOAE amplitudes and CAF-DPOAE amplitudes. Such a correlation could indicate a correlation in physiological properties between the characteristic places in the CAF range and the EHF range. For example, ears with stronger than average active amplification in the CAF range may have stronger than average active amplification in the EHF range. This could arise from both frequency ranges suffering from noise-induced damage due to broadband noise exposure.

3.7.4 Which stimulus level or condition can evoke greater EHF-DPOAEs and EHF-TEOAEs?

Two questions were tested: the first asked which parameters or paradigms yield OAEs with the greatest SNRs, and the second asked which parameters lead to OAEs that are most strongly correlated with EHF-HTLs.

The project tested two different stimulus levels ([65/55] and [70/70] SPL) for evoking EHF-DPOAEs, to identify which level pair evokes the greater amplitude and/or SNR, when analysed with a paired- t-test. Statistically significant differences between EHF-DPOAEs (65/55) and EHF-DPOAEs (70/70) were found after recording both SNR and amplitude, with the higher stimulus level (70/70) evoking higher measurements for EHF-DPOAEs. A comparison between R-values, found that the EHF-HTLs are more strongly correlated with the EHF-DPOAEs in the (65/55) paradigm than those in the (70/70) paradigm for both signal amplitude and SNR. In this study the (70/70) paradigm evoked greater amplitudes from EHF-DPOAEs, although EHF-HTLs were better predicted by EHF-DPOAEs at (65/55) than at (70/70), despite the fact that the SNRs were poorer for EHF-DPOAEs at (70/70). A greater response was elicited with EHF-DPOAEs at (70/70) compared to (65/50).

It was suggested by Poling et al. (2012) that higher stimulus levels of more than 70 dB SPL may allow greater opportunity to record EHF-DPOAE signals from a larger number of subjects, as SNR would increase with increasing primary level. However, this does not make this stimulus level more sensitive to cochlear dysfunction at the EHF, as further studies are needed to investigate the sensitivity. At the CAF range, the DPOAE signal amplitude has been found to increase approximately monotonically (i.e. it always goes up and never down as the stimulus level increases) with input levels of up to 75 dB (Dorn et al., 2001). Thus, a greater response for the high stimulus level was expected. If the stimulus levels are kept at the same dB SPL in the CAF region and the EHF region, then they will be lower in the EHF when expressed in dB HL (because the RETSPL is higher in the EHF region). Thus, they take no account of the higher RETSPLs in EHF region, which means that, on average, the sensation level of the primaries in the (70/70) paradigm will be considerably lower in the EHF than in the CAF region, due to the factors mentioned in section 2.3.2. This is one reason that the (70/70) paradigm might be more appropriate than the (65/55) paradigm for use in the EHF region.

On the other hand, no such statistically significant difference was noticed with the two different conditions used (HPF click and TB 10 kHz) for evoking EHF-TEOAEs. Similarly, when comparing the R-value the correlation of EHF-HTLs, with EHF-TEOAEs is the same regardless of the stimulus paradigms (TBs vs HPF), and for both signal amplitude and SNR.

3.7.5 Limitations of the cross-sectional study

- In this study the stimulus level was calibrated using the standard ear simulator method, which, due to EAC characteristics, can increase inter-subject variability for the EHF measurements. The study did not use FPLs, which may reduce the impact of the EAC effect, but this would have been time consuming and requires specialist equipment. Instead, the current study overcame the inter-subject variability by averaging the results of hearing measurements across frequency ranges. It also did not use the EPL method of measuring EHF-OAEs.
- In this study, the aim was to recruit subjects that were highly exposed to noise (such as students in the university music department), so that the sample population did not end up being skewed to the right due to having too few participants with high NESI scores, while the rest were concentrated to the left. But the nature of the study, such as the requirement for longitudinal data (Chapter 4) was an obstacle to recruitment as the subjects were required to come for follow-up testing twice after the baseline visit.
- The NESI score is calculated on self-reported measurements, so under- or overestimation of exposure levels by the subject could be a factor affecting the results.

3.8 Summary of Chapter 3

This study addressed three research aims, the first was to investigate the impact of noise exposure on CAF and EHF hearing (analysed with LMM and split-plot ANOVA). The second was to determine which parameters used to evoked EHF-TEOAEs and EHF-DPOAEs lead to the highest signal amplitudes and SNRs. The third aim was to assess the correlation of OAE measures with EHF-HTLs, and to find which OAEs are most strongly correlated with EHF-HTL.

3.8.1 CAF- and EHF-measurements sensitivity to NESI score: LMM

The outcome of average values (across frequencies) for CAF and EHF measurements were analysed with LMM (i.e. NESI score as a continuous covariate), to assess the effect of NESI score on the HTL in both CAF and EHF ranges. When age was included in the LMM as a covariate for all of the hearing measurements (HTL, TEOAEs, and DPOAEs), there was no statistically significant effect of age on the measurements of hearing, which was expected given the small range of ages in the sample.

For HTL, the results show that NESI score has a statistically significant effect on both CAF and EHF-HTL, the 7-frequency average CAF-HTL with an effect rate of 0.04 dB for each 1 unit of NESI score. Statistically significant interaction term of NESI score and frequency range, indicating that the effect of NESI score was greater in the EHF-HTL than the CAF-range, as with each increase of 1 unit of NESI score there was a rate of 0.21 dB increase in 5- frequency average EHF-HTL above the 7-frequency average CAF-HTL increase.

Analysis for both TEOAEs and DPOAEs were conducted for amplitude and SNR separately. For TEOAEs there were statistically significant effects of NESI score on the 7-band average CAF-TEOAEs amplitude and SNR; with 1 unit increase of NESI score there was a decrease in 7-band average CAF-TEOAE amplitude by 0.08 dB SPL and SNR 0.06 dB. There were no statistically significant variations in the 3-band average EHFs compared with CAFs in TEOAE amplitude and SNR, in association with NESI score. Furthermore, LMM showed that there were statistically significant effects of NESI score on 16-f2-average CAF-DPOAE amplitude using (70/70); with 1 unit increase in NESI score there was a decrease of 0.09 (dB SPL) amplitude. However, there was no statistically significant effect of NESI score on SNR at CAF and 4-f2-average EHF-DPOAE amplitude and SNR with (70/70). LMM showed DPOAEs at (65/55) were significantly associated with noise exposure at CAF in both amplitude and SNR; with 1 unit increase in NESI score there was a decrease of 0.10 (dB SPL) amplitude and 0.10 (dB) SNR. However, there were no variations between the amplitude and SNR for EHF-DPOAEs (65/55) above CAF range.

As well as including NESI score as a covariate (continuous predictor) in the LMM, NESI score was included in split-plot ANOVA as a IV (categorical predictor), as summarized in the following section.

3.8.2 Difference in EHF-measurements between low- and high- NESI groups: split-plot ANOVA

Split-plot ANOVA was also used to assess the effect of NESI score on hearing measurements. The sample was aligned to low- or high- NESI groups based on the median 50% pf NESI score, i.e. low-NESI (n=29) and high- NESI (n=29). There was no significant difference between groups at HTL, TEOAEs and DPOAEs (amplitude and SNR), although the high- NESI group sample had a high proportion of participants with low NESI score. An exploratory analysis was therefore conducted and subjects were split into four groups based on the IQRs of NESI score (low- NESI group: GP1 [n=14], GP2 [n=15] and high- NESI group: GP3 [n=15], GP4 [n=14]) to eliminate the impact of low scores in high- NESI group. So Gp 4, the highest high- NESI group, showed a higher proportion of higher NESI scores, and there were statistically significant main effect of NESI score on the high-NESI group for EHF-HTL, EHF-DPOAE amplitude, and EHF-TEOAE amplitude and SNR.

3.8.3 EHF-OAEs response evoked with different parameters

This study assessed the evoked EHF-TEOAEs and EHF-DPOAEs using different parameters. For the former, two stimulus waveforms were used (HPF and TB [10 kHz]); for the latter, two stimulus levels were used (low level [65/55] and high level [70/70]). The purpose of using different parameters was to determine which produced higher amplitudes and SNR and which was the better predictor of EHF-HTLs. There was a statistically significant difference between the (65/55) and the (70/70) levels for EHF-DPOAE amplitude and SNR, with EHF-DPOAEs at (70/70) having greater amplitude and SNR than EHF-DPOAEs at (65/55). However, the EHF-DPOAEs at (65/55) were found to correlate better with EHF-HTL than the EHF-DPOAEs at (70/70). For EHF-TEOAEs, there was no statistically significant difference between HPF and TB, but the value for HPF was higher than for TB (10 kHz), for amplitude and SNR. The EHF-TEOAEs for the two paradigms were very highly correlated (R=0.95) indicating little difference in the two measures when averaged over the EHF-range.

3.8.4 Association between EHF-measurements

Pearson's correlation for EHF-measurements showed that there was a significantly negative correlation between EHF-HTL and EHF-TEOAE amplitude and SNR and with EHF-DPOAE amplitude. In addition, there was a positive statistically significant correlation between EHF-DPOAE SNR and amplitude with EHF-TEOAE SNR and amplitude. This agrees with the findings of previous studies of the CAF range. EHF-DPOAE (65/55) was more strongly correlated to EHF-HTL (and is thus a better predictor) of EHF-HTLs than was EHF-DPOAEs (70/70) despite the latter giving better SNRs on average.

3.8.5 EHF-HTL prediction from EHF-OAEs

Comparisons of these correlations were made to assess which measurements of EHF-OAEs were better predictors of EHF-HTL. There were no statistically significant differences between the R-values of EHF-HTLs vs. EHF-DPOAE and vs. EHF-TEOAE amplitudes; both were likely to predict the EHF-HTL equally. For the SNR, the EHF-DPOAE SNR was not significantly correlated with EHF-HTL, while the R-value for the EHF-TEOAE SNR and EHF-HTL were statistically significant. For EHF-TEOAEs the differences between the R-values the correlation of EHF-HTLs, with EHF-TEOAEs (SNR and amplitude) is the same regardless of the stimulus paradigms (TBs vs HPF), might indicate that they predict EHF-HTL equally. (HPF).

Chapter 4 The longitudinal relationship between high frequency hearing and noise exposure (Study 1B)

4.1 Introduction

In Chapter 3 it was observed, from cross-sectional data, that measures of hearing status correlate with NESI score. Although an association between NESI score and hearing status was found from the baseline data, observational studies always carry the risk of confounding variables. For example, subjects who participate more frequently in activities with high noise exposure might differ in lifestyle (e.g. with regard to diet, alcohol consumption, and smoking) or socio-economic status from those who participate less frequently. The confounding effects of some variables are greater for cross-sectional studies than for longitudinal studies. For example, the age-related HTLs presented in ISO 7029:2017 and studies of EHF-HTLs at different ages (e.g. Lee et al., 2012) are based on cross-sectional studies, which might be affected by changes in noise regulations and lifestyle over time, as well as the effects of age. One way to focus specifically on the effects of age and noise exposure is to conduct a longitudinal study to monitor changes in hearing status over time, and to compare this with changes in age and noise exposure within subjects. The results of the cross-sectional research by Lee et al. (2012) imply that EHF-HTLs differ by over 1 dB per year in the 20–30 year age group, suggesting that changes in EHF-HTL could be detected over relatively short periods of 1 or 2 years in this age group (if age-related). Similarly, incremental noise exposure might lead to measurable changes in EHF-HTLs or other hearing measures.

The present research aimed to observe changes in hearing status as well as changes in NESI score over time, using a within-subject design. HTLs, TEOAEs, and DPOAEs at CAFs and EHFs were measured. The NESI questionnaire was administered over a period of up to 16 months, over three visits, to assess the association of incremental changes in hearing with changes in age and NESI score. Note that potential confounding variables (e.g. smoking status or socioeconomic status) that may be correlated with incremental NESI score could still not entirely be excluded using the design of this longitudinal study. A larger study would be required to control for such potential confounding variables. One advantage of the longitudinal design is that incremental NESI scores are less likely to be affected by memory recall errors than in the cross-sectional study.

The project plan had been to monitor hearing over at least 2 years; however, unforeseen problems with equipment, recruitment, drop-outs and covid restrictions led to these plans being revised. Due to the lockdown, once data collection for Phase 2 was over, any future scheduled testing was cancelled, ending up with a total sample size of 26 at that phase.

4.2 Research aim and research questions

Aim: To determine whether changes in EHF-hearing due to aging and noise exposure can be detected over a period of 6–16 months, using EHF-HTL, EHF-TEOAE and EHF-DPOAE measurements.

- RQ1. Can increase in EHF-HTL be detected in a group of young adults with a range of noise exposures over a 06–16-month period?
- RQ2. Can increase in EHF-DPOAEs and EHF-TEOAEs be detected in a group of young adults with a range of noise exposures over a 06–16 month period?
- RQ3. Are changes in EHF-HTLs and EHF-OAEs over a 06–16 months period related to NESI score over the same period?
- RQ4. How well do changes in the amplitude of EHF-OAEs predict changes in EHF-HTLs?

4.3 Methods

This longitudinal study was conducted over a period of 16 months, over three visits, to investigate the impact of noise and aging on EHF-hearing. Hearing measurements were collected at three time points over the study period (baseline and two follow-ups (F/U): Phase 1 and Phase 2). Changes in hearing up to 8 month period were investigated by analysing data from the first two time points (baseline and Phase 1), while changes in hearing up to 16 months were monitored using data from all three time points: baseline, Phase 1, and Phase 2. The plan was to follow up the entire sample (n=58) analysed in Chapter 3 (which was at the baseline, i.e. Timepoint 1), with each participant assessed every 6 to 8 months over a period of 16 months. However, it was difficult for some of the participants to commit to the planned assessment schedule; instead, each assessment was determined based on participant availability. It is worth mentioning that with longitudinal studies, there is a danger of high participant dropout rate, which was the case in this study. Unfortunately, this challenge occurred throughout the experiment, partly as a result of enforced Covid-19 lockdowns.

The exact measurements of HTLs, TEOAEs, DPOAEs, and NESI scores were taken using the techniques described in Section 3.3.

In the analysis of LMM, to minimize the effect of missing data, the full data set was analysed for each phase instead of using LMM directly to overcome the missing data. The reason for not doing the latter was that in phase 2 there was a large dropout rate, so including the missing data within the LMM might add uncertainty to the analysis. Moreover, the missing data may also be correlated with the outcome measures. This is because subjects who drop out may be the ones with the highest noise exposure because both may be correlated with socioeconomic group.

4.3.1 Sample size calculation

The calculation of the sample size for the baseline data was made as described in Section 3.3.1. The present section deals with the detection of changes in EHF-HTLs due to aging and/or noise exposure from baseline measurements and subsequent measurements gathered over a period of 1.5 years. It was assumed that EHF-HTLs would increase over time with increase in noise exposure and/or age. Two assumptions were proposed according to the two variables, i.e. age and noise exposure, each one with a different assumed sample size.

4.3.1.1 **Detecting changes in EHF HTLs due to aging**

Lee et al. (2012) found that EHF-HTLs are likely to change by approximately 1.15 dB per year. To detect any changes in EHF-HTL due to age, the standard deviation in HTL was estimated from the test-retest reliability of HTL, following Schmuziger et al. (2004), who reported that about 85% of ears had a test-retest difference of < 5 dB. They did not directly report the test-retest standard deviation but this can be estimated from the percentage of measurements with a difference of < 5 dB, if it is assumed that the difference between test and retest HTL is normally distributed. From this assumption, the standard deviation of the difference in test-retest HTLs can be shown to be 5 dB/1.5 = 3.33 dB. Because the outcome measure is an average HTL over the six frequencies in the EHF range, it can be shown that the standard deviation of the frequency-averaged test-retest is 3.33 dB/sqrt(F), where F is the number of frequencies (F=6 here, including 18 kHz). Hence the test-retest measurement error (standard deviation) of the frequency-averaged HTL outcome measure is 3.33/sqrt(6) = 1.39 dB. The sample size calculation was then conducted assuming a paired t-test with a change in mean HTL with age of 1.15 dB per year, with a standard deviation of the change (due to test-retest error) of 1.38 dB. To observe changes over time for one year, 15 participants were needed, and for over 16 months, 8 subjects were required (Table 4.1). Sample sizes were calculated based on alpha = 0.05; power = 80%; 2 tailed test.

Table 4.1: To detect changes due to aging, the required sample sizes are based on alpha = 0.05; power = 80%; 2-sided test; F= 6 frequencies, paired t-test

Years	Changes in Mean (dB)	Assumed Std Dev of change (dB) = sigma * sqrt (2/F)	n
1	1.15	1.39	15
1.5	1.72	1.39	8
2	2.3	1.39	6

From Table 4.1, it was calculated that to detect incremental change in EHF-HTL of 1.72 dB over 1.5 years due to age, a minimum of 8 subjects is required.

4.3.1.2 **Detecting changes in HTL due to incremental noise exposure**

A further sample-size calculation was performed for detecting the differences between high- and low-noise exposure groups with respect to incremental changes in HTL over time. A between-group comparison was designed to investigate the impact of noise on hearing by assessing whether there is a difference between low- and high- NESI groups in the EHF-HTL shift over 1.5 years, due to differences in NIHL between groups. The effect of NIHL was estimated from Liberman et al. (2016), who reported differences in EHF-HTL between high-risk and low-risk groups of 9 dB at age 22 years. Assuming that the noise exposure in their study was accumulated over approximately 9 years of teenage and young-adult years, the growth in difference is about 1 dB per year. Table 4.2 was based on this assumption. The between-subject variance in the change in HTL measured over 1.5 years has two main components: test-retest measurement error and inter-subject differences in age- and noise-associated hearing loss. These have been roughly estimated to be 3.33^2 dB and 0.2^2 dB respectively. After taking account of the effect of frequency averaging over 6 EHFs, these two components combine to give an estimated standard deviation of the change in HTL within both the noise-exposure groups of $\text{sqrt}(0.2^2 + 3.33^2/6) = 1.4$ dB. The estimated required sample sizes in Table 4.2 are based on an independent samples t-test (for 80% power, 5%-alpha, 2-tailed test).

Table 4.2: To detect differences between noise-exposure groups in incremental changes in HTL over time, the sample sizes are calculated based on alpha = 0.05; power = 80%; 2-sided test; F = 6 frequencies, independent sample t-test.

Years	Noise induced changes in mean HTL over time (dB)	Assumed Std Dev of freq average HTL shift (dB) in each group	N per group
1	1	1.4	32
1.5	1.5	1.4	15
2	2	1.4	9

From Table 4.2, to detect a 1.5 dB difference between groups in noise-induced incremental change in EHF-HTL over 1.5 years, 15 subjects in both groups are required.

It is worth mentioning that the initial sample size calculation was based on averaging 6 frequencies including 18 kHz, but after the results were obtained it was decided not to include the 18 kHz in the average due to a large amount of missing data at that frequency, as mentioned in Chapter 3.

4.4 Results

Data was collected over a period of up to 16 months from those who participated in the initial study and from those who returned for the following two visits (see Table 4.3).

Table 4.3: Number of subjects included in the repeated measurements and their age mean (baseline, Phase1, and Phase 2), the mean of NESI score and changes of NESI from previous measurement.

Visits	Participants	Baseline NESI score, mean (SD)	Final NESI score, mean	Changes from previous measurement	Age at the measurement point, mean (SD) (years)
Phase1	43	13.29 (15.4)	13.91	0.62	24.74 (4.87)
Phase2	26	13.09 (15.39)	13.73	0.64	24.92 (4.43)

4.4.1 Descriptive statistics

Table 4.4 shows the descriptive statistics of the three time points, the 7 frequency-average CAF-HTL and 5 frequency-average EHF-HTL. Table 4.5 shows CAF-OAEs and EHF-OAEs in terms of mean and SD. The former is expressed in dB HL and the latter in dB SPL for signal amplitudes and dB for SNR.

Table 4.4: Mean/SD for CAF and EHF-HTL, for the baseline, Phase 1, and Phase 2. Note that the CAF-HTL was averaged over 7 frequencies (0.5, 1, 2, 3, 4, 6, and 8kHz) and the EHF-HTL was averaged over a 5-frequency range (10, 11.2, 12.5, 14, and 16 kHz)

Measurement	Baseline Mean (SD)	Phase 1 Mean (SD)	Phase 2 Mean (SD)
CAF (dB HL)	2.74 (2.9)	2.7 (2.64)	2.58 (3.23)
EHF (dB HL)	10.4 (10)	10.5 (8.55)	12.23 (9.06)
Subjects included	58	43	26

Table 4.5: Baseline, Phase 1, and Phase 2 Mean/SD for CAF-DPOAE (averaged across 16 frequencies (1, 1.1, 1.3, 1.5, 1.7, 2, 2.3, 2.6, 3, 3.5, 4, 4.6, 5.3, 6.1, 7, and 8.1 kHz) and EHF-DPOAEs (averaged across 4 frequencies (9.3, 10.7, 12.3, and 14.1 kHz) and CAF-TEOAE (averaged for quickscreen ILO ½-octave bands frequencies (0.7, 1, 1.4, 2, 2.8, 4, and 5.65 kHz) and EHF-TEOAEs (averaged across 3 ½-octave bands with centre frequency (6.7, 9.4, and 13.3 kHz).

Measurement	Baseline Mean (SD)	Phase 1 Mean (SD)	Phase 2 Mean (SD)
CAF-DPOAEs Amplitude (using 70/70) (dB SPL)	22.03 (4.30)	21.81 (4.12)	20.67 (4.48)
EHF-DPOAEs Amplitude(using 70/70) (dB SPL)	12.28 (4.71)	11.59 (5.16)	11.48 (4.0)
CAF-DPOAEs SNR (using 70/70) (dB)	25.71 (6.67)	24.86 (5.65)	24.20 (6.75)
EHF-DPOAEs SNR (using 70/70) (dB)	21.11 (4.57)	20.11 (4.85)	20.46 (4.43)
CAF-TEOAEs Amplitude (dB SPL)	20.15 (5.53)	20.43 (5.57)	18.76 (6.18)
EHF-TEOAEs Amplitude (using HPF) (dB SPL)	8.39 (5.9)	8.58 (5.09)	7.22 (6.72)
CAF-TEOAEs SNR (dB)	22.12 (5.69)	21.68 (5.77)	20.33 (6.62)
EHF-TEOAEs SNR (using HPF) (dB)	7.22 (5.73)	7.93 (4.86)	6.40 (6.63)
Subjects included	58	43	26

4.4.2 Changes in HTL over time

This section assesses RQ1 (see Section 4.2). The research hypothesis is that noise exposure is associated with HTL, especially at EHF, and that the EHF-HTL deteriorates over time with incremental noise exposure more so than the CAF-HTL. This hypothesis is tested using LMM.

The analysis model was set up as follows to model the differences in HTL between the baseline and each of the two f/u phases in turn. The model included four terms, that was selected to estimate the main aim and to fit the number of samples. The first term was β0, which indicates the change in HTL in the CAF range. ARHL is known to preferentially affect EHF compared to CAF. The Beta1 term indicates the additional change in HTL in the EHF region over and above that in the CAF region. The Beta2 term is the change in the HTL in the CAF region due to the increase in NESI score. The Beta3 term is the change noise-induced change in HTL over and above that in the CAF region.

However, it was decided that there were not enough satisfactory observations to support a model with six parameters. It is recommended that there are between 10 and 20 observations for each parameter in the model (Twisk, 2019). There were only 52 observations in the model (26 subjects × 2 frequency regions). For this reason, only the four most important parameters were included in the model.

$\Delta HTL_{ij} = \beta_0 + \beta_1 \times FreqRange_j + \beta_2 \times \Delta NESI_i + \beta_3 \times \Delta NESI_i \times FreqRange_j + \varepsilon_{ij}$

where ΔHTL_{ij} is the difference in HTL between the chosen f/u time point and the baseline (the two f/u time points are modelled separately). The subscript i is the subject ID and j is the index to the two frequency ranges, j (0 = CAF; 1 = EHF). The intercept term, β_0 indicates the systematic change in HTL at CAFs due to causes unrelated to noise exposure over the two time points. This is expected to be changes due to aging alone. β_1 is the change due to aging alone at EHFs over and above any change at CAFs and EHFs (equally). $\beta_2 \times \Delta NESI_i$ indicates the change in HTL at CAFs and EHFs due to the change in incremental increase in NESI score between the two time points. $\beta_3 \times \Delta NESI_i \times FreqRange_j$ indicates the additional change in HTL at EHFs due to the change in incremental increase in NESI score between the two time points at EHFs over and above any change at CAFs. The term ε_{ij} is the error term estimated by the residual. The model was run in SPSS using the residual ε_{ij} with an unstructured covariance matrix to allow for correlated residuals across the two frequency ranges.

4.4.2.1 **HTL over a period of 6 to 8 months between the baseline and follow-up Phase 1**

Changes in HTL over up to 8 months were investigated between 2 time points (baseline and Phase 1) in n= 43 participants who were present at both time points (following the drop-out of 15 subjects from baseline). Table 4.6 shows the results of LMM for the two time points. The results show no statistically significant main effect or interaction term, indicating that no changes in HTL between the baseline and Phase1 were seen in either CAF or EHF ranges, either due to age or incremental NESI score.

To directly test the statistical significance of adding the interaction term in β_3 to the model (which indicates that the effect of the change in NESI score is different in the two frequency regions), the values of "-2log(likelihood)" for the model with and without β_3 were compared against a chi-square distribution to assess whether the change in log(likelihood) was greater than would be expected by change with interaction term to model (Twisk, 2019). It was found that adding an interaction term to the model did not lead to a significant improvement of the model, indicating that changes in NESI score could not be related to changes in HTL for the two frequency regions.

The line graph in Figure 4.1 shows the difference between HTL at the baseline and the HTL after 6 to 8 months (Phase 1). At two frequencies (10 and 11.2 kHz), the HTL reduced over the time interval by more than might be expected from test-retest reliability, though this change was not statistically significant for the average in the EHF region. It is speculated here that this may be due to a problem in the stability of the HDA200 headphones which was not detected despite regular calibration. It may indicate that maintaining the calibration to better than 1 or 2 dB is difficult for these headphones with the current ear simulators. Note that the required accuracy of calibration is better than that required for clinical calibration, where the tolerances range from ± 3 dB to ±5 dB depending on frequency**.** A study by the German national standards body found that the Sennheiser HDA200 headphones and reference ear simulator show a sensitivity to temperature, atmospheric pressure and relative humidity that might potentially have led to changes of a few decibels that might not be controlled for in the current study (Richter, 2003).

Table 4.6: Changes in HTL reported by the LMM analysis for the baseline and Phase 1, showing P-values and beta coefficients

Increase in HTL (dB HL)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-0.06	0.78
EHF vs. CAF over time, β_1	0.10	0.42
CAF and EHF association ΔNESI, β_2	0.27	0.64
EHF vs. CAF association ΔNESI, β_3	-0.42	0.19

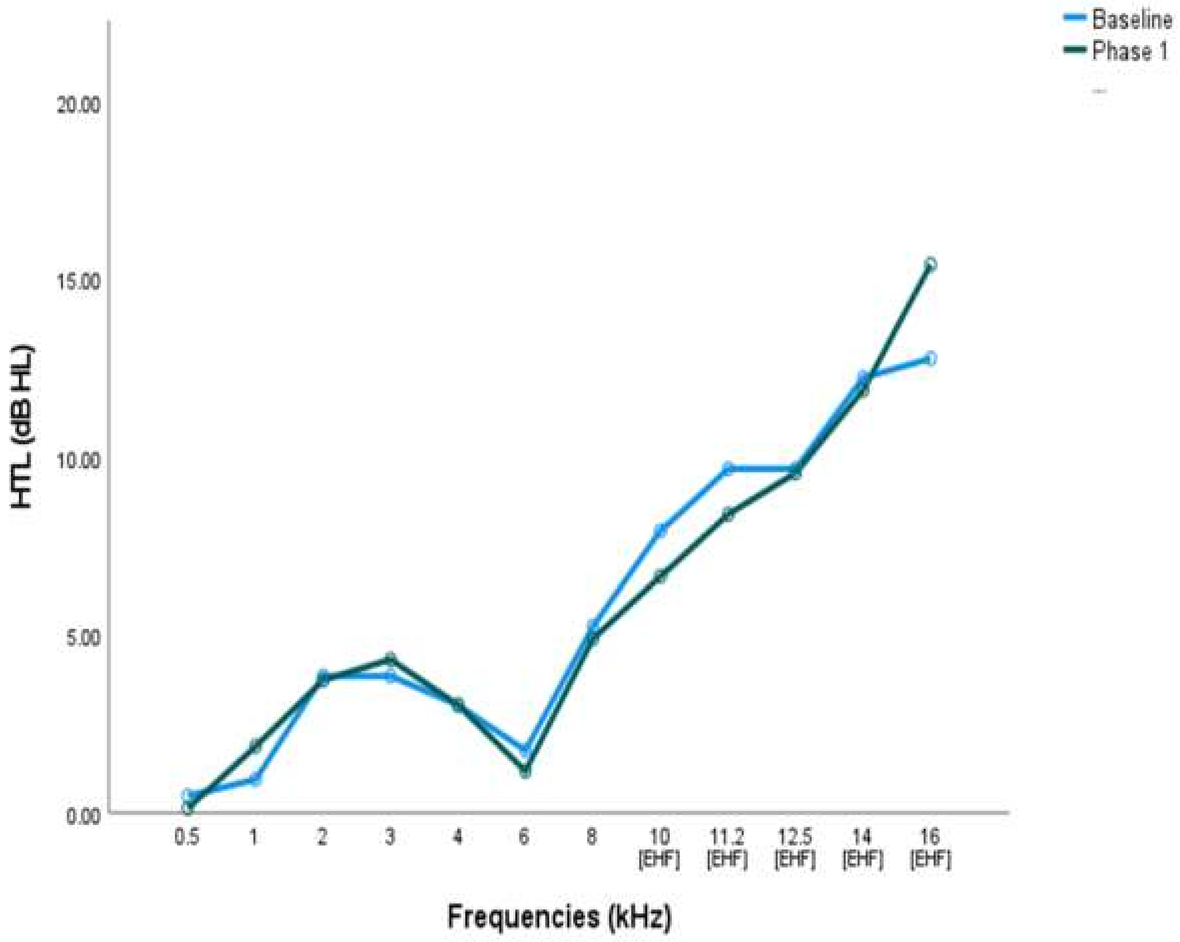


Figure 4.1:The line graph shows the mean of HTL (dB HL) across the sample, over 6–8 months, at baseline (blue line) and Phase 1 (green line); data for the mean across 43 subjects.

4.4.2.2 Changes in HTL over a period of 12–16 months between baseline and Phase 2

Table 4.7 shows the analysis of data collected from baseline and last f/u, over 12–16 months, which, after subject drop-out from baseline (32 subjects) and other reasons (see Section 4.1), left n = 26 participants.

The results for β_0 showed a statistically significant difference at CAF and EHF which is unrelated to noise exposure, but was in the unexpected direction: the HTL appeared to reduce over the period by approximately 1.07 dB. There was also a small but statistically significant effect of frequency range (β_1), indicating that EHF-HTL increased by about 0.31 dB relative to the CAF-HTL over the period of time. There was also a small but statistically significant effect of the incremental increase in NESI score at EHF (β_3), also in an unexpected direction, but no significant values for β_2, suggesting no difference in CAF due to noise exposure. It is speculated that the apparent reduction in HTL over time may have been due to instabilities in the transducers that were not detected by the calibration. The line graph in Figure 4.2 shows the difference between HTL at the baseline and the two f/u.

Table 4.7: Changes between the baseline and Phase 2, measured by LMM analysis, showing P-values and beta coefficients

Increase in in HTL (dB HL)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-1.07	<0.05
EHF vs. CAF over time, β_1	0.31	<0.05
CAF and EHF association ΔNESI, β_2	1.30	0.13
EHF vs. CAF association ΔNESI, β_3	-0.75	<0.05

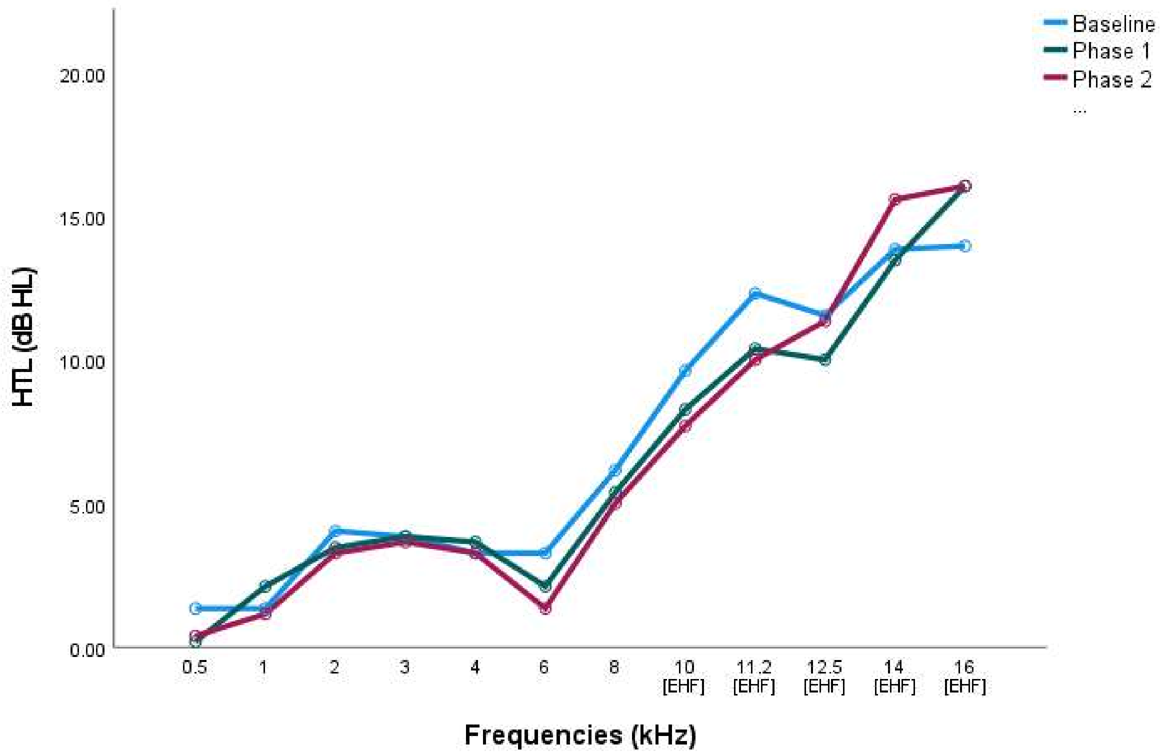


Figure 4.2: The HTL (dB HL) over a period of 12–16 months (total of 3 visits with gaps of 6–8 months between each visit) for the baseline (blue line), Phase 1 (green line) and Phase 2 (red line); data for the mean across 26 subjects.

As in Section 4.4.2.1, the statistical significance of adding the interaction term in β_3 to the model was assessed using the change in "-2log(likelihood)" for the model with and without β_3 (Twisk, 2019). It was found that adding an interaction term to the model did lead to a significant improvement of the model, indicating that changes in NESI score could be related to changes in HTL for two frequency regions.

4.4.3 Changes in TEOAEs over time

To answer RQ2 (see Section 4.2) a similar hypothesis to that for HTL was tested for TEOAEs. It was also hypothesised that noise exposure impacts emissions, especially at EHFs, and that the EHF-TEOAEs deteriorate over time with continuous noise exposure more than the CAF-TEOAEs.

As for HTLs, LMM analysis was also applied to the TEOAE amplitudes and SNRs. LMM was run separately for each SNR and amplitude.

4.4.3.1 TEOAEs changes over a period of 6–8 months (baseline and Phase 1)

To assess TEOAEs over a period of up to 8 months, LMM was conducted to investigate how the amplitude and SNR might change due to time. Table 4.8 A and B below show the results of LMM interpretation of changes in TEOAEs between the baseline and Phase 1. There were no statistically significant main effects or interaction term involving phase, indicating that no changes in TEOAE amplitudes or SNR between the baseline and Phase 1 were seen in either CAF or EHF ranges, either due to age or incremental NESI score.

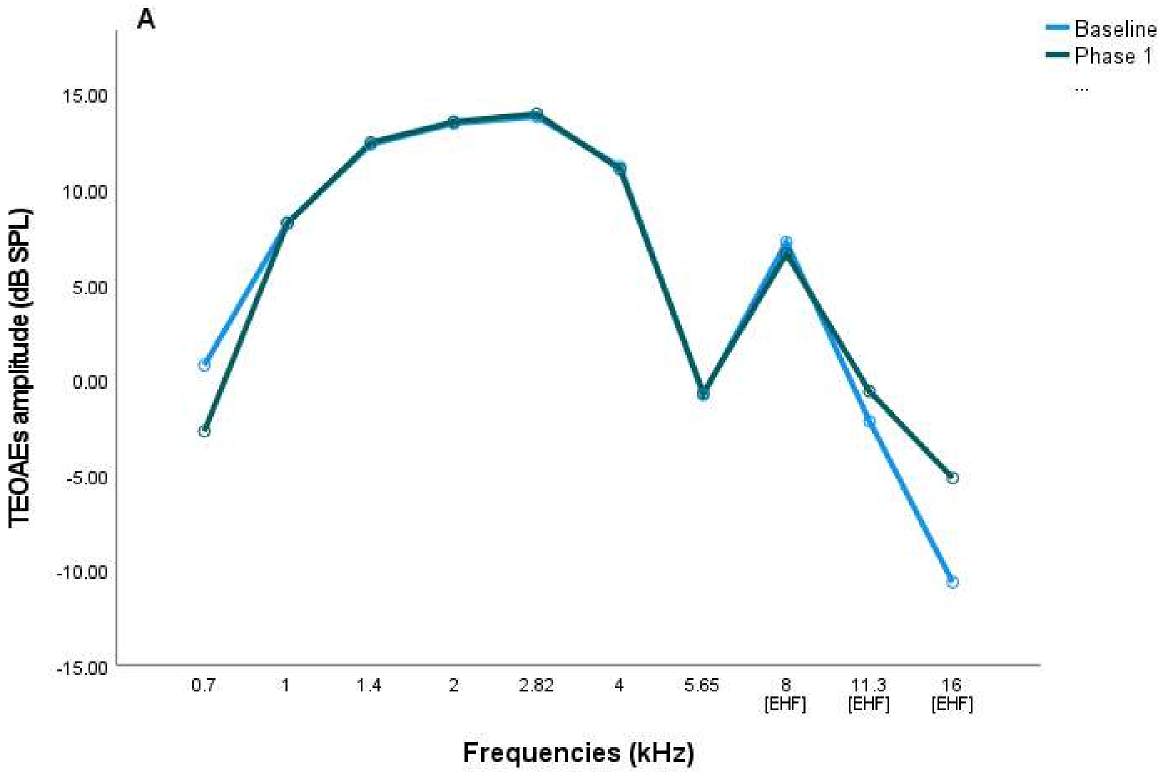
The line graphs in Figure 4.3 A and B show the difference between TEOAEs at the baseline and after 6 to 8 months (Phase 1).

Table 4.8 A: Changes in TEOAE amplitude (using HPF) from the p values reported by LMM analysis for the two visits: baseline and Phase 1.

Increase in amplitude (dB SPL)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	0.34	0.51
EHF vs. CAF over time, β_1	-0.53	0.06
CAF and EHF association ΔNESI, β_2	-0.55	0.44
EHF vs. CAF association ΔNESI, β_3	0.34	0.39

Table 4.8 B: Changes in TEOAE SNR (using HPF) from the p values reported by the LMM analysis for the two visits: baseline and Phase 1.

Increase in SNR (dB)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-0.21	0.74
EHF vs. CAF over time, β_1	-0.35	0.31
CAF and EHF association ΔNESI, β_2	0.57	0.53
EHF vs. CAF association ΔNESI, β_3	0.24	0.63



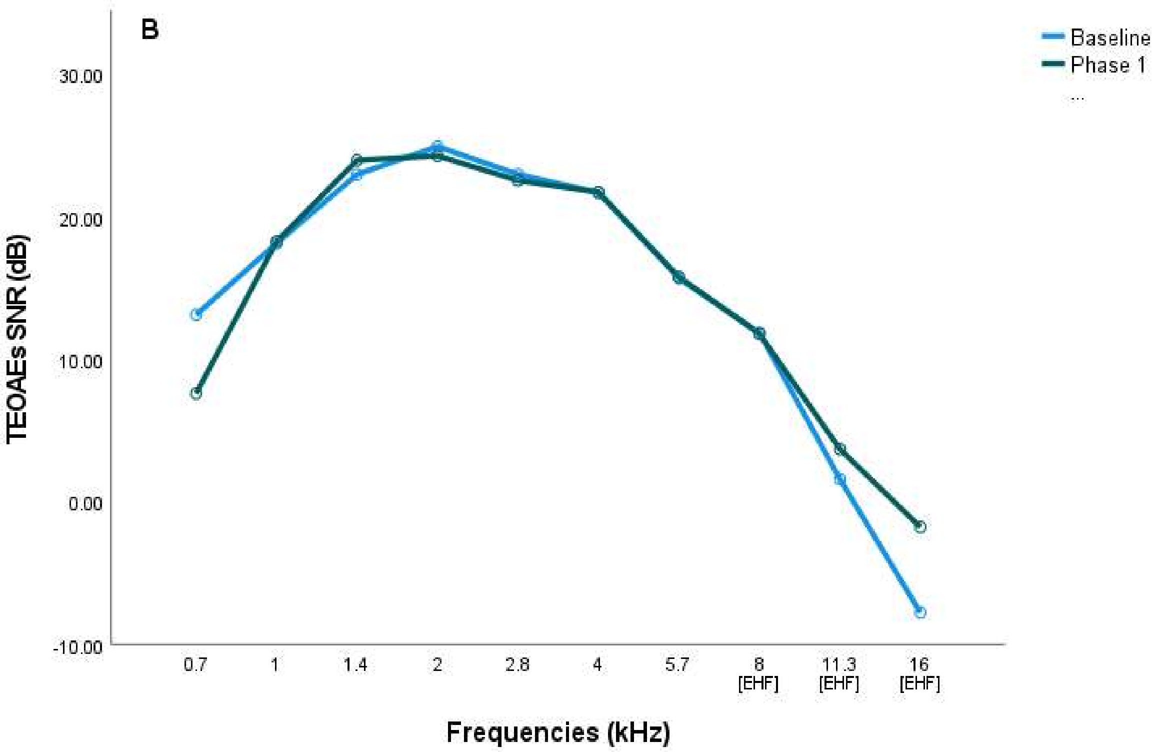


Figure 4.3 A and B: The line graphs shows the TEOAE (A) amplitude (dB SPL) and (B) SNR (dB), over a period of 6–8 months, at the baseline (blue line) and Phase 1 (green line); data for the mean across 43 subjects.

4.4.3.2 **TEOAEs over a period of 12–16 months for 2 visits (baseline and Phase 2)**

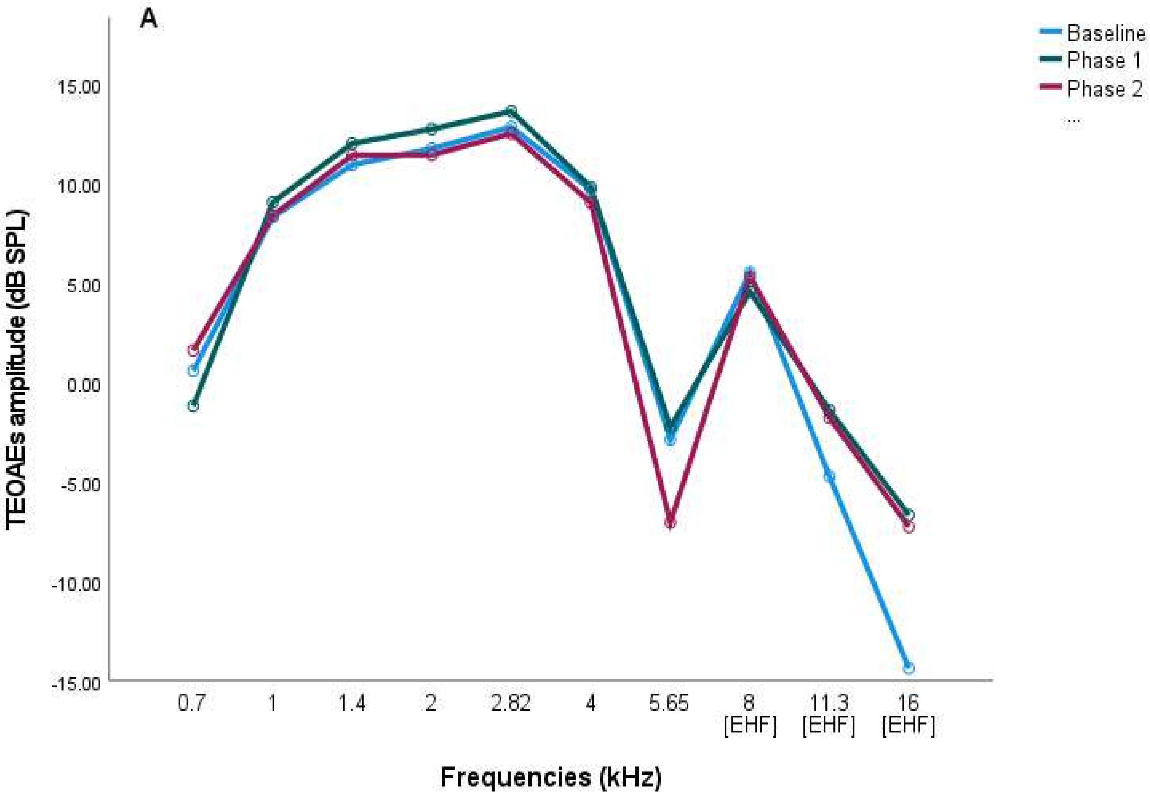
Changes in the amplitude of the TEOAEs and SNR over time were assessed by LMM. Table 4.9 A and B show data at the baseline and Phase 2, collected over a period of up to 16 months. No statistically significant values for β_0 and β_2 were found, suggesting no main effect or interaction term involving frequency range, indicating that no changes in TEOAEs between the baseline and Phase 2 were seen in CAF, either due to age or incremental NESI score. Moreover, there were no significant values for β_1 and β_3, indicating no difference in EHF range (compared to CAF range) due either to aging or noise exposure. The line graphs in Figure 4.4 A and B shows the difference between the TEOAEs of the baseline and the TEOAEs in Phase 2, after 12 to 16 months.

Table 4.9 A: Changes in TEOAE amplitude (using HPF) from the p values reported by LMM analysis for the three visits: baseline and Phase 2.

Increase in amplitude (dB SPL)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-0.16	0.75
EHF vs. CAF over time, β_1	-0.03	0.85
CAF and EHF association ΔNESI, β_2	-0.21	0.83
EHF vs. CAF association ΔNESI, β_3	0.21	0.51

Table 4.9 B: Changes in TEOAE SNR (using HPF) from the p values reported by the LMM analysis for the three visits: baseline and Phase 2.

Increase in SNR (dB)	Beta coefficients	P-value
CAF and EHF over time, β_0	-0.039	0.96
EHF vs. CAF over time, β_1	-0.38	0.23
CAF and EHF association ΔNESI, β_2	0.07	0.96
EHF vs. CAF association ΔNESI, β_3	0.55	0.22



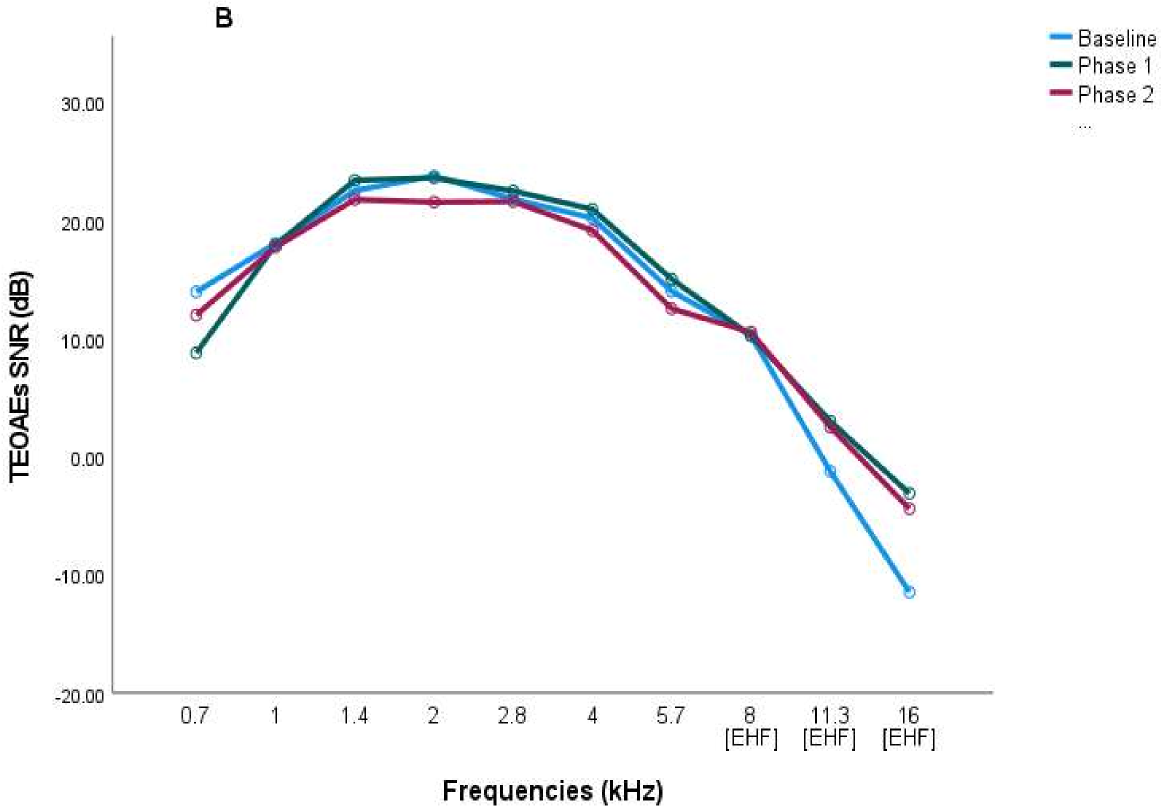


Figure 4.4: A and B: The line graphs show the TEOAE (A) amplitudes (dB SPL) and (B) SNR (dB) over a period of 12–16 months (total of 3 visits with a gap of 6–8 months between each visit) at baseline (blue line), Phase 1 (green line) and Phase 2 (red line); data for the mean across 26 subjects.

4.4.4 Changes in DPOAEs due to noise exposure

LMM was also conducted in order to test for changes in DPOAEs (RQ2). The same model and interpretation of LMM analysis was applied as for HTL and TEOAEs. LMM was run separately for each SNR and amplitude.

4.4.4.1 DPOAE changes over a period of 6–8 months for 2 visits (baseline and Phase 1)

Changes in DPOAE amplitudes and SNR between the baseline and Phase 1 were measured. The LMM results are shown in

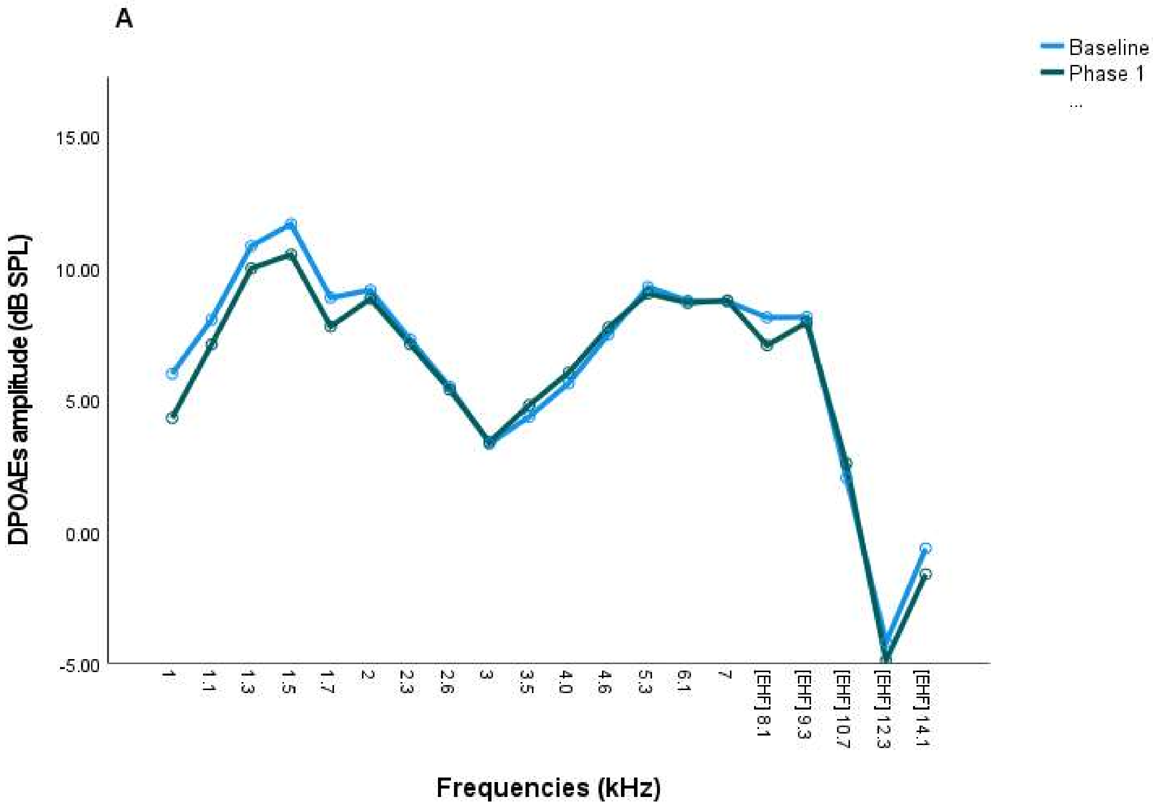
Table 4.10 A and B. The results showed no statistically significant main effect or interaction term of frequency range. This suggests that there were no observable changes in DPOAE amplitudes and SNRs between the baseline and Phase 1, either for CAF or EHF ranges, either due to age or incremental NESI score. The line graphs in Figure 4.5 A and B show changes between the DPOAEs measured at the baseline and after up to 8 months.

Table 4.10 A: DPOAE amplitude (using 70/70) changes from the p values found by the LMM analysis for the two visits: baseline and Phase 1.

Increase in amplitude (dB SPL)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-0.32	0.46
EHF vs. CAF over time, β_1	0.11	0.63
CAF and EHF association ΔNESI, β_2	-0.52	0.33
EHF vs. CAF association ΔNESI, β_3	-0.19	0.50

Table 4.10 B: DPOAE SNR (using 70/70) changes from the p values found by the LMM analysis for the two visits: baseline and Phase 1.

Increase in SNR (dB)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-1.03	0.29
EHF vs. CAF over time, β_1	0.43	0.40
CAF and EHF association ΔNESI, β_2	-0.22	0.85
EHF vs. CAF association ΔNESI, β_3	-0.83	0.19



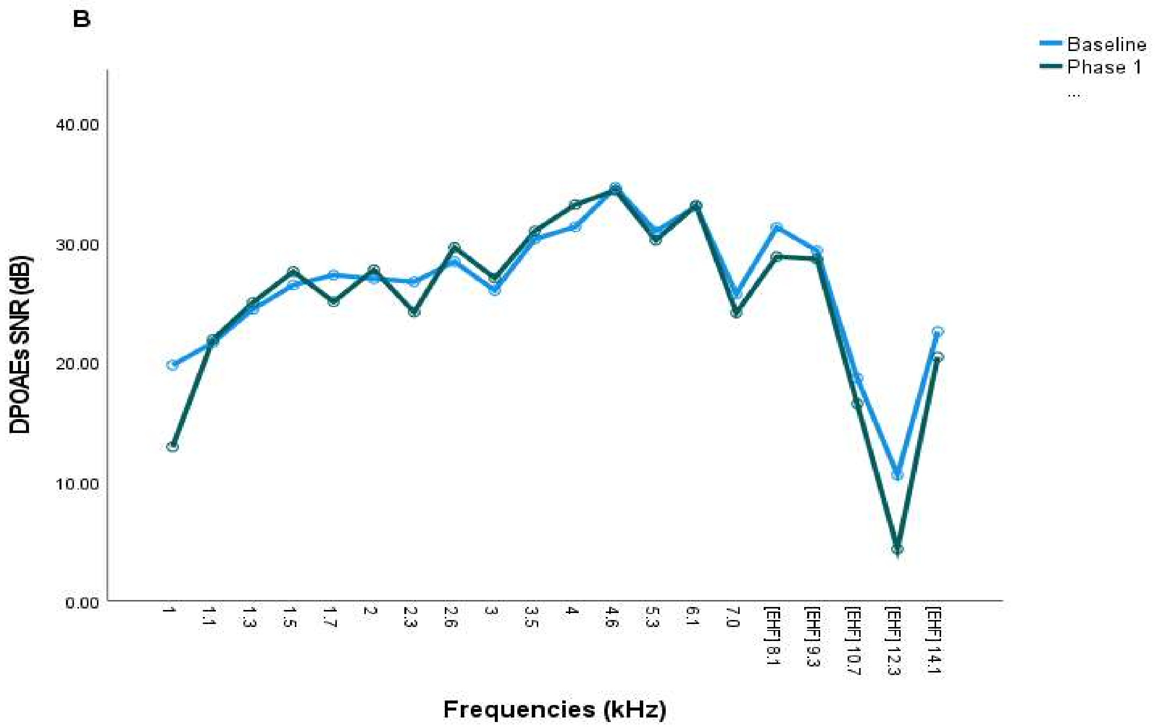


Figure 4.5 A and B: The line graphs show the DPOAE (A) amplitudes (dB SPL) and (B) SNR (dB) over a period of 6–8 months between baseline (blue line) and Phase 1 (green line); data for the mean across 43 subjects.

4.4.4.2 **Changes in DPOAEs over a period of 12–16 months between baseline and Phase 2**

Changes in DPOAE amplitude and SNR over up to 16 months were analysed by LMM; the results are shown in Table 4.11 A and B. The DPOAEs amplitude and SNR did not show statistically significant main effects either from age or the incremental increases in NESI score, either at CAF or EHF range. There was no interaction term involving frequency range, suggesting no changes between the baseline and Phase 2. The line graph in Figure 4.6 A and B shows changes between the DPOAEs of the baseline and the DPOAEs after up to 16 months (Phase 2).

Table 4.11 A: DPOAE amplitude (using 70/70) changes from the p values reported by the LMM analysis for the three visits: baseline and Phase 2**.**

Increase in HTL (dB SLP)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-0.65	0.17
EHF vs. CAF over time, β_1	-0.02	0.89
CAF and EHF association ΔNESI, β_2	0.40	0.52
EHF vs. CAF association ΔNESI, β_3	0.16	0.41

Table 4.11 B: DPOAE SNR (using 70/70) changes from the p values reported by the LMM analysis for the three visits: baseline and Phase 2.

Increase in SNR (dB)	**Beta coefficients**	**P-value**
CAF and EHF over time, β_0	-1.76	0.11
EHF vs. CAF over time, β_1	-0.70	0.05
CAF and EHF association ΔNESI, β_2	1.55	0.20
EHF vs. CAF association ΔNESI, β_3	0.43	0.26

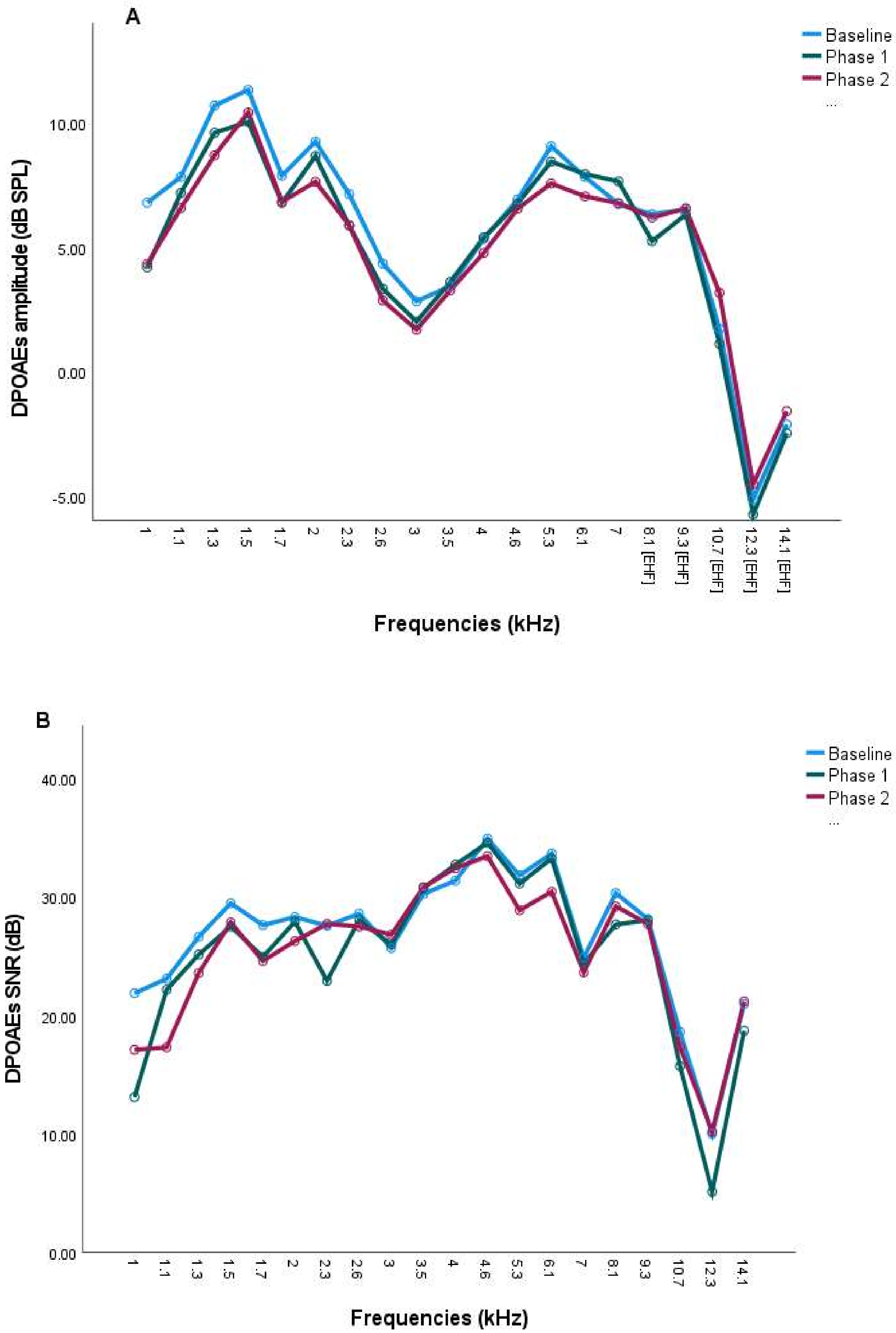


Figure 4.6 A and B: The line graphs show the DPOAE (A) amplitudes (dB SPL) and (B) SNR (dB) over a period of 12–16 months (total of 3 visits with a gap of 6–8 months between each visit) at the baseline (blue line), Phase 1 (green line) and Phase 2 (red line); data for the mean across 26 subjects.

As in Sections 4.4.2.1 and 4.4.2.2, assessment of RQ3 (Section 4.2) for OAEs, the statistical significance of adding the interaction term in β_3 to the model was also assessed using the change in "-2log(likelihood)" for the model with and without β_3. It was found that adding an interaction term to the model did not significantly improve the model, indicating that changes in NESI score could not be related to changes in either TEOAEs or DPOAEs for two frequency regions (Appendix D).

4.4.5 Prediction of changes in EHF-HTL from changes in EHF-OAEs measurements

One of the research questions was how well changes in EHF-OAEs can predict changes in EHF-HTLs (RQ 4, Section 4.2). Pearson's correlation was conducted to assess how the changes in EHF-OAEs (amplitude and SNR) correlate with changes in EHF-HTL (Table 4.12), including the data from the final f/u (Phase 2). The reason behind only including the final f/u was that it covers a more extended period of up to 16 months. Therefore, there might be more cumulative changes in hearing that can be potentially assessed between measurements. The results show no statistically significant correlation between changes in EHF-DPOAEs, EHF-TEOAEs and EHF-HTL, either for amplitude or SNR. There was a statistically significant positive correlation between changes in EHF-TEOAEs (amplitude and SNR) and changes in EHF-DPOAE amplitude, although no similar significant correlation was seen with changes in EHF-DPOAE SNR. Such correlation between changes in TEOAEs and changes in DPOAEs was expected, as both measurements share similar generation mechanisms. However, they could also arise from any un-detected change in calibration which would affect both OAE measures to a similar degree.

Table 4.12: The correlation between changes in EHF-DPOAEs (70/70) and changes in EHF-TEOAEs (HPF) with changes in EHF-HTL, between baseline and phase 2 (N = 26).

Pearson Correlation	EHF-HTL	(70/70) DPOAEs amplitude	(70/70) DPOAEs SNR	HPF TEOAEs amplitude	HPF TEOAEs SNR
EHF-HTL	1				
(70/70) DPOAEs amplitude	-0.34	1			
(70/70) DPOAEs SNR	-0.38	0.69**	1		
HPF TEOAEs amplitude	-0.14	0.53*	0.24	1	
HPF TEOAEs SNR	-0.15	0.51*	0.26	0.99**	1

Correlation is significant at 0.01**
Correlation is significant at 0.05*

4.5 Discussion

In the current study, changes in HTLs and OAEs in association with incremental NESI scores were assessed over 16 months, and an evaluation was made of whether EHF-range could add any additional information to the CAF-range measurements.

4.5.1 Effect of incremental increases in NESI score on HTL (CAF and EHF)

The current study assessed the changes in HTL at two time intervals; the first was over the 6–8 months between the baseline and Phase 1. The second was over 12–16 months between the baseline and Phase 2.

4.5.1.1 Changes in HTL over a period of 6–8 months

There were minor changes in HTL over a period of up to 8 months, but changes were not statistically significant, indicating that no reliable changes in HTL between the baseline and Phase1 were seen in either CAF or EHF ranges, either due to age or incremental NESI score.

It was expected that there would be no discernible variation between phases in the CAF-range, either due to age or increase in NESI score, based on previous studies. One explanation for expecting no changes is that CAF-ranges are thought to be unaffected by age for frequency > 6kHz start, especially when subjects are as young as 30 years (Lee et al., 2012). On the other hand, although it has been suggested that age affects EHF-range, a similar effect was not reported in the current study. This varies from previous studies, which suggest that EHF-HTL are affected by aging, and elevation in EHF HTL was seen even in young populations (Lee et al., 2012; Jilek et al., 2014). For example, Lee et al. (2012) reported that HTL above 14 kHz is about 6–15 dB higher for the age group 22–35 years, compared to the age group 10–21 years, although HTLs lower than 8 kHz were similar for both groups. One possible reason for not seeing similar effects due to age on EHF-HTL is related to the limited age range (< 35 years) of the sample population. In addition, comparing the findings of the current time intervals with previous studies was difficult due to the minimum duration (up to 8 months) for HTL progression.

Previous studies have found little between-group (noise-exposed and non-exposed) HTL differences for CAF-range (Liberman etal.2016; Ahmed et al., 2001), although differences have been observed in the EHF-range. There are possible explanations for why there were no significant findings in CAF-range between phases due to age and NESI score in the current study. One reason for this may be related to the time interval (up to 8 months) between the baseline and Phase 1. With this shorter duration between the first and second test, changes in HTL may not have been detected, as they can take years to develop. Moreover, the current study design only included subjects with CAF-HTL ≤ 20 dB HL, and therefore changes in CAF-HTL might not be present in the current sample.

The theory proposed here is that EHF-HTL is associated with NESI score, i.e., that incremental increase in NESI score is associated with an increase in HTL at EHF range; however, the current study did not observe any significant association in this regard. A reason for not seeing changes due to incremental NESI score might be related to the sample of the current study. For example, most of the subjects were students in the UoS and data were collected during an academic year, in which they may have spent more time in the library than in nightclubs. These conditions may have resulted in less noise exposure than normal, and, therefore, a lower NESI score. The sources of noise for this sample population may not have been sufficient to cause significant changes in HTL, as seen in other studies where subjects were exposed to occupational noise sources (Ahmed et al., 2001). Another possible reason is that estimating lifetime noise exposure using the NESI score could result in overestimation of exposure to noise, as these measurements are mainly subjective and self-reported.

4.5.1.2 **Changes in HTL over a period of 12–16 months**

LMM for the second time interval (between baseline and Phase 2) over 12–16 months showed statistically significant differences due to age at CAF-HTL; unexpectedly, the changes between baseline and Phase 2 at CAF-HTL were in the opposite direction, showing that over up to 16 months, Phase 2 results decreased by about 1.07 dB from the baseline. There are several reasons why that was the case in the current study. A possible reason for the difference in CAF-HTL may have been because of instabilities in the transducers (HDA200) that were not detected by regular calibration. Moreover, it has been suggested by Richter (2009) that the HDA200 headphones, as well as the ear simulator, are subject to changes of a few dB due to their sensitivity to temperature, atmospheric pressure, and relative humidity, which were not controlled for in the current study. Another reason might be due to type 1 error, which maybe due to negative pressure in ME that has been recovered in the F/U. Therefore, as with measurement in the EHF range, caution should be taken with calibration and any factor that might cause variation in measurement such as ME anomalies.

There was also a small but statistically significant effect at EHF over a period of 1.5 years: about a 0.31 dB rate of increment in HTL for up to 16 months. This is less than what was expected; Lee et al. (2012) reported a rate of 1 dB/year at the EHF-HTL. The current study varies from the previous mentioned study in the calibration method in which they took account of the effects of individual ear-canal acoustics. Thus, this might give an indication that the ear canal characteristic can impact the EHF HTL and accounting for the ear canal characteristic might be useful for more reliable results.

There was a significant effect at EHF-HTL due to noise exposure, but again this was in an unexpected direction, showing a decrease of about 0.75 dB in HTL at the EHF between baseline and f/u after 16 months (Phase 2). The changes in noise exposure were statistically significantly associated with changes in EHF-HTL over the period of time. One reason for seeing an unexpected decrease in changes in HTL at EHF due to incremental NESI score might be due to calibration, as detailed above.

4.5.2 Effect of incremental increases in NESI score on OAEs (CAF and EHF)

CAF-OAE responses are thought to change with noise exposure (LePage and Murray,1998; Montoya et al., 2008) and with age (Lonsbury-Martin et al., 1991; M Yu et al., 2019; Satoh et al., 1998). Changes have been hypothesised to be faster in the EHF range than in the CAF range. The current study used LMM to assess changes in SNR and amplitude of both TEOAEs and DPOAEs at CAF and EHF for the first and second intervals. The findings showed no statistically significant effects of NESI and no changes in amplitude or SNR (CAF and EHF) were seen between the baseline and Phase 1, nor between the baseline and Phase 2, either due to age or incremental increases in NESI score. This finding differs from Seixas et al. (2005) and Lapsley Miller et al. (2004), who reported a statistically significant decrease in DPOAE amplitude of about 0.5 and 0.9 dB per year at CAF. Lapsley Miller et al. (2004) also reported a reduction of 0.6 dB per year in CAF-TEOAE amplitude due to noise exposure and 0.7 dB/year due to age. However, no changes were reported for CAF-DPOAEs over a year period. Not seeing any changes in emission over time might be due to several reasons. One reason may have been potential due to instabilities in the SPL calibration produced by the probe, that were not detected by regular calibration.

Deterioration in hearing with prolonged and repeated exposure to noise is gradual and increases most during the first 10–15 years of exposure for CAF-HTL (Kirchner et al., 2012). After that, the degree of HL due to noise exposure might reach a plateau, even with constant exposure. In the current sample, the subjects were young, and their maximum years of exposure are assumed to be up to 7 years. Despite this assumption, the age range of the young adults included in the present study would be sufficient enough for possible noise exposure effects. Despite this, there were still no observable changes in amplitude, even with an increase in NESI score. It could have been that higher NESI scores were the result of subjective over-estimation by the participants, leading to scores that did not match the actual noise exposure. Alternatively, it would have been that the changes in NESI score were too small to cause a detectable change in OAE amplitude.

Another reason for lack of EHF-OAE change with NESI may be the dependency of cochlear emissions on the ME. The ME attenuation might make it less likely to detect EHF-OAE at all, as there is greater ME attenuation of OAEs at EHFs than CAFs. Yet, if the OAEs are measured simultaneously and then measured again a year later after some NIHL, then the ME attenuation (in dB) will be same in both cases, so changes should be able to be detected. Unless, however, there are slight changes in ME status over time that may mask the effects of cochlear changes.

4.5.3 The correlation between changes in EHF measures over time

The Pearson correlation was calculated for Phase 2 results, to assess whether or not changes in EHF-OAE amplitude are correlated with changes in EHF-HTL. No significant correlations were reported between changes in EHF-OAEs and changes in EHF-HTL, although there was a statistically significant correlation between changes in EHF-DPOAE amplitude and changes in EHF-TEOAE amplitude, indicating that increases in EHF-DPOAEs were associated with increased amplitude EHF-TEOAEs. However, there was no correlation between changes in EHF-DPOAE SNRs and changes in EHF-TEOAE SNRs. One possible explanation for this lack of association between SNRs, is that this measurement can be affected by other variables, such as noise.

4.6 Summary of chapter 4

This longitudinal study aimed to investigate changes in HTL and OAEs from data collected over 3 separate visits, over a period of time up to 16 months. In analysing the data changes over a period of 6–8 months, the findings show that HTL did not change between the baseline readings and Phase 1 readings. Monitoring changes over a period of up 16 months between the baseline and Phase 2 showed statistically significant differences in CAF-HTL due to age and noise exposure, but in the unexpected directions. In addition, there were statistically significant differences in EHF-HTL that related to noise exposure, but no significant changes in EHF related to aging. It is possible that these small but statistically significant changes over time may have been the result of errors in calibration, particularly in the EHF region. There were no changes in amplitude or SNR between the first and second intervals for CAF and EHF (TEOAEs and DPOAEs). In hindsight, the detection of small changes of 1 to 2 dB over time may indicate that better control is needed of factors such as environmental temperature or calibration equipment which can lead to systematic errors that are not reduced by averaging either over frequency or subjects. There was no correlation between changes in EHF-HTL and changes in EHF-OAE, but there was a positive correlation between changes in EHF-TEOAE and changes in EHF-DPOAE amplitudes.

Chapter 5 Study two: Transient otoacoustic emissions and audiogram fine structure in the extended high-frequency region

5.1 Overview

Chapter 5 addresses Study 2, which aims to establish whether there is a relationship between EHF-PTA with both the AFS ripple depth and TEOAEs, all at EHFs (8–16 kHz). In particular, this experiment will examine if similar associations seen in the CAF-range are present in the EHF-region.

5.2 Introduction

A normal hearing CAF audiogram, when measured with small frequency intervals, shows a quasi-periodic pattern of peaks and valleys (ripples) called the AFS; the ripples are stable over time (Elliott, 1958; Long, 1984; Long and Tubis, 1988; Thomas, 1975). The cycles are present as a consistent pattern (called the threshold microstructure), with peaks of good sensitivity (minimum threshold) and valleys of poorer sensitivity (maximum threshold). Elliot (1958) was the first to discover the phenomenon of AFS and described it as the "rippling effect". On average these ripples illustrate a patten of spectral periodicity observed and quantified by the frequency separation of Δf, between the nearby peaks, and the geometric mean centre frequency, fc, of two peaks. It was estimated that the average value of $fc/\Delta f$ is about 15; that is, equivalent to a frequency interval of 6.7% or 10.7 cycles per octave (Kemp, 1979; Schloth, 1983; Kapadia and Lutman, 1999; Lutman and Deeks; 1999).

Studies have reported correlations between AFS spectral periodicity and OAE properties, such as the minimum spacing between spontaneous otoacoustic emissions (SOAEs), and the delays of stimulus frequency (SFOAEs) and transient TEOAEs (Kemp, 1979; Probst et al., 1986; Schloth, 1983; Zwicker and Schloth, 1984; Dallmayr, 1987; Kapadia and Lutman, 1999; Lutman and Deeks; 1999; Dewey and Dhar; 2017). It has been suggested that the correlations arise from cochlear mechanical behaviour (Talmadge et al., 1998; Zweig and Shera, 1995).

A cochlear mechanical theory of TW propagation and reflection on the basilar membrane has been suggested to explain for the relationships between these phenomena. Zweig and Shera (1995) predicted a correlation between the spectral periodicity phenomena of AFS and some of the properties of OAEs. The forward TW becomes amplified by OHC activities as it approaches its characteristic frequency place and then becomes partially reflected due to the random inhomogeneity; a backward TW is then generated. When the backward TW reaches the stapes, it will be further partially reflected, generating a second forward TW which well be reflected again to generate another backward wave, and so on. This action leads to an interference pattern between the forward and backward TW, at the frequencies where the two waves come in-phase. The excitation at the characteristic place is enhanced, leading to a dip in the audiogram where the threshold becomes lower than would have occurred in the absence of any reflection. At such frequencies, the cochlea sometimes becomes unstable, resulting in SOAE in the EAC that is generated by the number of backward TWs which are partially transmitted through the ME. Therefore, both AFS and SOAEs require active amplification and multiple TW reflections in the cochlea.

TEOAE and SFOAE generation also requires active amplification of the OHCs and at least one apical reflection close to the characteristic place to generate backward propagating wave components, resulting in components reflected in the EAC that can be recorded by a probe. However, subsequent reflections from the stapes, followed by multiple reflections, are not necessary for the existence of OAEs, though multiple reflections will affect the spectrum of these evoked OAEs. The theory predicts that, at a given stimulus frequency, the delay in SFOAE- and TEOAE-components relative to the evoking stimulus are also related to $fc/\Delta f$ and hence are related to the spectral periodicity seen in AFS and SOAEs (Figure 5.1). This model also predicts that the ratio of $fc/\Delta f$ is related to the location frequency mapping length and the TW wavelength near the peak area, which in turn is related to the sharpness of TW tuning (Zweig and Shera, 1995; Talmadge et al., 1998; Shera, 2003). In theory, if the cochlea were to show a property known as "scaling-symmetry", then the ratio $fc/\Delta f$ would be independent of frequency (Zweig and Shera, 1995). However, the measurements of AFS ripple and SOAE spacing, along with SFOAE delays, suggest that the ratio $fc/\Delta f$ increases from approximately 8 to 20 between 0.5 and 7 kHz, corresponding to a change in frequency interval from 5.9 to 14.2 cycles per octave (Shera 2003). Thus, these changes imply that the cochlea does not show "scaling-symmetry", but that it deviates somewhat from this symmetry. In this model, an increase in sharpness of tuning of the TW peak with stimulus frequency could explain why the cochlea deviates from symmetry scaling in this way (Shera et al., 2002; Shera and Guinan, 2003; Shera, 2003).

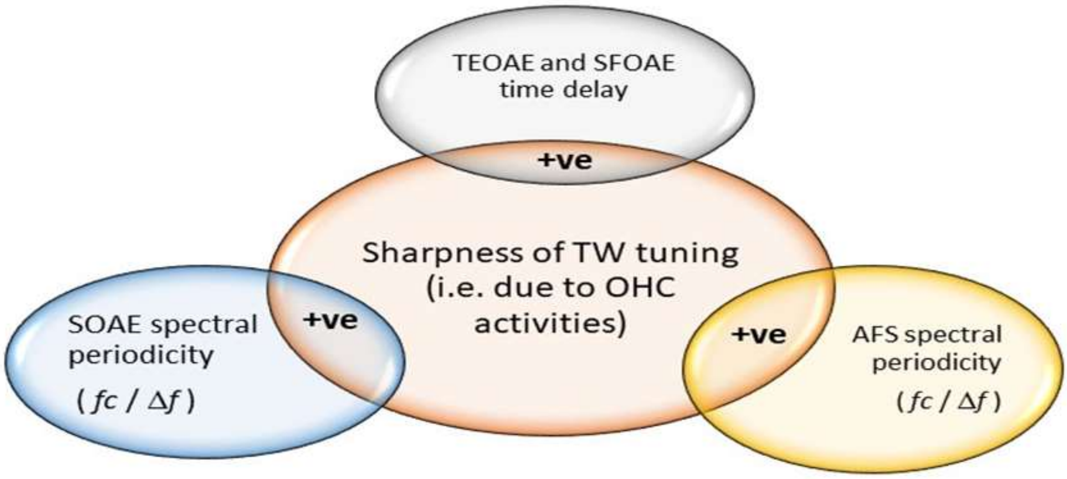


Figure 5.1: Diagram showing the predicted correlations between measurable periodicities and cochlear mechanical properties according to the theory of travelling wave reflection from distributed inhomogeneities along the basilar membrane. +ve correlation is predicted between sharpness of TW tuning due to strength of OHC activity and with the ASF and SOAE spectral periodicity ($fc/\Delta f$) and TEOAE and SFOAE time delay.

According to the multiple-reflection theory, three mechanisms are required for generating AFS. First, active cochlear amplification, second, TW reflection at the base and, third, TW reflection at apical sites. In the current study, as well as AFS, the HTL i.e. PTA-HTL and TEOAEs was also examined. In theory, the PTA-HTL are expected to be affected by active amplification (greater amplification leading to lower HTLs), but are expected to be largely independent of multiple reflections due to averaging across frequencies. This independence is mainly because the multiple reflections lead to constructive interference at some frequencies and destructive interference at others, and hence do not affect the average HTL across a frequency range that encompasses several spectral periods of the AFS.

However, it is predicted that TEOAE amplitudes share their generation from two mechanisms with AFS i.e. the active amplification and the apical reflections of TW. From this, the current study expected the TEOAE amplitudes and the AFS-ripple depth to be strongly correlated, more so than frequency-averaged HTLs that only share one generative mechanism with band-averaged TEOAE amplitude i.e. active amplification. Kapadia and Lutman (1999) showed that individuals with relatively strong TEOAE amplitudes had greater AFS-ripple depth than those with absent or weak TEOAEs, when variation in HTL was controlled (Table 5.1). Horst et al. (2003) also found reduced AFS-ripple depth as average HTLs increased.

As in Chapters 3 and 4, the outcome measures of EHF-HTL and EHF-TEOAEs were averaged based on averages across several frequencies that were analysed. These are termed the 6-frequency-average HTL and TEOAE band-average for the EHF (further details on outcome averaging are explained in Section 5.7.2.1). The theoretical predictions of measurement correlation based on cochlear behaviours (i.e., of TW reflection from distributed inhomogeneities along the basilar membrane) are summarised in Table 5.2.

Table 5.1: Predicted measurable correlations assuming variability in the potency of apical reflections within the population (assuming OHC activity is constant).

Metric	**Predicted Correlation due to potency of apical TW reflections**	
	Average HTL over one octave	Average TEOAE amplitude over one octave
Ripple depth of AFS	0	+ve[1]
Average HTL over one octave	1	0
Average TEOAE amplitude over one octave	0	1

[1] Reported by Kapadia and Lutman et al. (1999) when variation in HTL was controlled.

Table 5.2: The predicted correlations between the amplitude of measurable quantities and cochlear mechanical properties.

Metric	**Theoretical Predicted Correlation**		
	Strength of OHC activity	Potency of apical reflection site near TW peak	Potency of multiple reflections between apical reflection site and basal site at stapes
Average HTL over one or more octaves	−ve	0	0 or weak
Ripple depth of AFS	+ve	+ve	+ve
SOAE amplitudes	+ve	+ve	+ve
Average TEOAE and SFOAE amplitude over one or more octaves	+ve	+ve	0

Table 5.3 shows theoretical predictions of measurement correlation when assuming that there is variability in the strength of OHC activity. Correlation was well established and seen from clinical

testing (e.g. the higher HTLs are associated with low TEOAEs and AFS). Such correlations have been reported by Horst et al. (2003), where AFS was correlated with HTLs at EHFs.

Table 5.3: Predicted measurable correlations assuming variability in the strength of OHC activity within the population (impact of potency of apical reflections is constant).

Metric	**Predicted Correlation due to strength of OHC activity**	
	Average HTL over one octave	Average TEOAE amplitude over one octave
Ripple depth of AFS	−ve[1]	+ve
Average HTL over one octave	1	−ve
Average TEOAE amplitude over one octave	−ve[2]	1

[1].Reported by Horst et al. (2003).
[2].Well established from clinical diagnostic testing.

Previous observations of these phenomena are generally based on measurements at frequencies at CAF-range, with very few measurements from studies reported on EHF. This may be due in part to the fact that OAEs in the EHF-range are difficult to measure — this is likely to be related to ME transmission function i.e. greater attenuation of TEOAEs in the EAC (Puria, 2003). Another difficulty in measuring the EHF-TEOAEs is that they have shorter OAE delays (information recorded in shorter latency), which makes it more difficult to separate the TEOAE signal from the stimulus artefact. However, separating the signal from the stimulus can be achieved using a low-artefact DE paradigm that reduces the effects of transducer non-linearity by using two earphones (Keefe, 1998 and Goodman et al., 2009) (see Sections 3.4.3.2 and 6.3.2). A time window domain of separate frequency bands was also used to eliminate the impact of noise on TEOAE response, with shorter latency for higher frequency (Goodman et al., 2009). Another complication with EHF-OAEs is the occurrence of standing waves in the EAC when measuring the EHF-region of OAEs. Consequently, both inward propagation of the stimulus and outward propagation of the OAE are affected, which can lead to errors in the estimates of both the stimulus level and the OAE level (Charaziak and Shera, 2017).

Hearing thresholds in the EHF-region can also differ in their characteristics compared to CAF. One of such difference is that the EHF-HTL shows a steep rise in SPL (i.e. the minimum audible pressure) with increasing frequency (Lee et al., 2012; Rodríguez Valiente et al., 2014; ISO 389-7, 2019). A further additional difference is that EHFs show greater influence of inter-subject differences in EAC acoustics (Moller et al., 1995; Souza et al., 2014) and also show greater inter-subject variability in HTLs in otologically normal ears (Schmuziger et al., 2005; Lee et al., 2012; ISO 28961, 2012). While the ME forward transmittance reduces steeply with increasing frequency in the EHF-region (Puria, 2003), the extent to which the properties of the cochlea differ in this region is unclear. However, psychophysical tuning curve measurements in the EHF region (Yasin and Plack, 2005) suggest that HTLs are determined by on-frequency rather than off-frequency listening, suggesting that a fully-formed cochlear TW is established at frequencies of up to at least 18 kHz. In addition, the sharpness of psychophysical tuning is similar to that at lower frequencies (Yasin and Plack, 2005). This suggests that the phenomena responsible for AFS at CAF may also occur in the EHF-region.

In addition to cochlear theory that lead to AFS, the EAC acoustical standing waves in the EHF region may also contribute to peaks and troughs in the audiogram. For instance, peaks in TM pressure associated with half-wave resonances typically occur at around 8 and 16 kHz for insert earphones (Charaziak and Shera, 2017). The influence of half-wave resonance can be reduced when expressed on a dB HL scale in audiogram and AFS. This is because the dB HL scale uses the RETSPL (reference equivalent sound pressure level) as the (frequency-dependent) reference pressure, and the RETSPL is obtained from the median detection threshold in the otologically normal population. If the otologically normal population all had EAC resonances at the same frequency, then no peaks and troughs due to EAC resonances would appear in the HTL when expressed on a dB HL scale. Thus, any peaks and troughs in the AFS due to EAC resonances will arise only where the acoustical properties of the individual's EAC differ from the median properties in the young otologically normal population. Furthermore, the peaks in an audiogram due to EAC resonances will have a considerably greater frequency spacing than that which arises in the AFS of cochlear origin. At between 8 and 16 kHz the frequency spacing is around 1 cycle per octave (Charaziak and Shera, 2017), compared to the expected 10.7 cycles/octave for AFS. Hence, any ripple in the AFS due to EAC acoustics can be readily separated from ripples of cochlear origin.

5.3 Rational for the study

AFS is one phenomenon where there is a paucity of evidence at EHFs, and which is affected by various aspects of cochlear mechanics. The properties of AFS are affected by the degree of travelling wave amplification, the sharpness of tuning of the travelling wave envelope, and reflections of the TW from both the characteristic place and from the stapes. These cochlear mechanical properties also affect SOAEs, TEOAEs and their relationship to AFS (Zweig and Shera, 1995; Talmadge et al., 1998). The question addressed in this study is therefore: do we see the same properties of AFS EHFs as we see at CAFs?

There is a paucity of knowledge on how the cochlear mechanism behaves in the most basal region. Therefore, it is not fully understood how the cochlear mechanism behaves in EHF hearing and if the correlation between measurements at EHFs is similar to what was seen in CAF hearing. The nature of these correlations is stated in more detail in section 5.1.

If a similar correlation at the EHF between AFS and OAEs properties was reported, it would mean that the cochlear mechanism behaves in a similar way in the basal region as in the apical region. On the other hand, when there is no correlation reported, as found in the current study, this may be due to the following. There is a difference between the AFS at EHFs and CAF, in that at EHF the ripple depth of the AFS is smaller in amplitude and less regular in its spectral periodicity than is seen at CAF. There are several possible causes for this: first, there is less OHC activity; second, there are less potent reflection sites near the characteristic place; third, the shape (width) of the TW envelope leads to less coherent reflection at the characteristic place (since the strength of the reflection depends on the width of TW envelope (Zweig and Shera, 1995); fourth, there is less basal reflection of the TW at the stapes.

5.4 Aims and research questions

The objective was to establish whether phenomena seen at the EHF-range are similar to those of CAF, i.e., whether there is discernible spectral periodicity in the AFS ripple, whether (across individuals) the ripple-depth would increase as EHF-TEOAE amplitudes increased, and whether the ripple-depth would decrease as frequency-averaged EHF-HTL increased (see Table 5.3). The aim and research questions are as follows.

Aim: To assess whether TW reflection mechanisms at EHFs region show similar properties to those at CAFs

RQ1: Was there a correlation between AFS ripple depth and HTL-PTA at EHFs?

RQ2: Was there a correlation between AFS ripple depth and TEOAE amplitude at EHFs?

RQ3: Does the AFS show distinctive regular spectral periodicity at the expected spectral interval?

The rationale for these two aims is to test the assumption that the correlations found at CAF (Kapadia and Lutman, 1999) are also found at EHF.

5.5 Methods

5.5.1 Sample size calculation

The aim was to recruit 26 participants for testing, in order to detect whether there was a correlation between the AFS and PTA in the EHF-region. Previous studies were consulted to ascertain an adequate sample size that could detect a correlation coefficient of 0.5 between the two measurements. It worth mentioning that previous study findings were based on CAF AFS measurements. Horst et al. (2003) were able to detect a significant negative correlation coefficient of r = 0.84 between sum peak heights and the average PTA threshold. In order to obtain a correlation of 0.5, a sample sizes of 26 participants was required based on alpha = 0.05, power = 80% and the 2 tailed test.

5.5.2 Participants

Normal hearing subjects were recruited from the University of Southampton using poster advertising as well as word of mouth and email. As shown in
Table 5.4, 28 subjects participated. One ear was tested per subject (the ear with the greatest CAF-TEOAEs, based on the OAE amplitude in dB SPL from the Otodynamics ILO 292 in "quickscreen" mode). All the participants satisfied the inclusion criteria listed in Section 3.3.2.1. Ethical approval was provided by University of Southampton Ethics and Research Governance Online (reference number: 40092.A1).

Table 5.4: The number of participants and their mean age and gender.

Number of Subjects	Ages (years) included	Age (years) mean	Male	Female
28	21- 40	28.8	10	18

5.6 Equipment and procedure

The following equipment was used to assess hearing, and all measurements were conducted in a sound treated double-walled room, in a single session that lasted for 1.5 hrs. The following hearing measurements were obtained. First, manual PTA (following the British Society of Audiology (BSA) recommended procedure) at 8, 10, 11.2, 12.5, 14, and 16 kHz; second, AFS using high-resolution Bekesy audiometry from 8–16 kHz; third, TEOAEs at frequencies up to 16 kHz using a DE paradigm, and fourth, SOAEs. Other OAE measurements were made during the same session as part of a separate study, as described in Chapter 6.

5.6.1 Manual PTA for frequencies from 8 to 16 kHz

The test was conducted using the same equipment and procedures as described in Section 3.4.1. Similarly, PTA-HTLs were measured at CAF and EHF following the standard BSA procedure (BSA, 2011) with a 5 dB step size. EHF-HTLs were obtained at 8, 10, 11.2, 12.5, 14, and 16 kHz. HTL measurements were repeated at 14 kHz to check reliability.

Six-frequency-average PTA-HTLs for EHF were calculated over the six audiometric frequencies given above 8–16 kHz, which will tend to average out the effect of inter-subject differences due to EAC acoustics. The reason that this reduces the effect of ear-canal acoustics is that the range of frequencies of half-wave resonances (which lead to differences with the population in the frequencies of the peaks and troughs in the HTLs) will be encompassed by the octave range used to calculate the average. The average was calculated as the arithmetic mean of the PTA-HTLs expressed in dB HL.

It worth noticing that the 5 dB step size does not limit the smallest detectable difference in the 6-frequency-average PTA-HTL, because the band average will have a quantization precision of 0.83 dB (see Appendix E for details).

5.6.2 High-resolution Bekesy Audiometry from 8 to 16 kHz.

The equipment described in Section 3.4.1 was used to present the stimulus. Bekesy audiometry was used to measure the AFS for the frequency range 8–16 kHz, which was split into two spans of 8–11 kHz and 11–16 kHz, to allow the participants a rest break (Table 5.5). The two sweep rates were different in Hz/sec, but each was chosen because they achieve similar sweep rates in log-frequency change/sec. Pilot studies were conducted before carrying out the main study, and the frequency step-rate was chosen accordingly. The stimuli comprised tone pulses of 220 ms duration, including 35 ms onset and offset ramps, followed by 220 ms silences.

Each participant was instructed to press a response button when they heard the tone-pulses and release it when they could not. The response button was connected to the computer, and the signal amplitude was changed at a rate of 3 dB/sec either up or down, depending on whether the response button was pressed or not. The AFS measurement procedure was then repeated to yield two replicates.

Table 5.5: Frequency stimulus, step rate, and sweep duration in the fine structure audiogram

Frequency stimulus (kHz)	Step rate (Hz/per sec)	Sweep duration (min)	Stimulus type (pure tone)
8–11	9	6	Continuously sweeping frequency.
11–16	12	7	

5.6.3 EHF TEOAE and SOAE measurements

The evoking stimuli for TEOAEs were presented using the equipment described in Section 3.4.3. As outlined in Chapters 3 and 4, EHF-TEOAEs were elicited by the DE method (Keefe, 1998), using HPF clicks as described in Sections 3.4.3.2 and 3.4.3.1. TEOAEs were also evoked using default clicks (with rectangular waveform) to provide descriptive information at CAF, though these measurements were not used in subsequent hypothesis tests. The measurements were repeated a second time for both HPF and default clicks, and recording was continued for approximately 70 sec per replicate test.

During piloting, the risk of stimulus artefact was assessed by two methods. First, EHF-TEOAE measurements were conducted after reducing the stimulus levels by 10 dB to check if the TEOAEs were genuine rather than stimulus artefacts. Second, recordings were also performed in an occluded ear simulator to assess the risk of stimulus artefacts that might contaminate the early time window, and to check whether that contamination was fully eliminated by the DE paradigm.

EHF OAE measurements are influenced by EAC resonances, which may affect the level of the evoking stimulus reaching the tympanic membrane (TM), and the level of the OAE signal recorded by the probe microphone (Charaziak and Shera, 2017). Stimulus calibration is described in Section 2.8.1.

The ER-2 earphone frequency response is relatively flat when measured in the ear simulator that is intended to reproduce the TM pressure of an average ear. However, the ear simulator is only designed to match the average adult EAC up to 10 kHz; for frequencies above that, the ear simulator is likely to become unrepresentative of an average ear (IEC 60318-4; 2010). Furthermore, the ear simulator differs from individual ears to differing degrees, leading to variation in the spectrum of the stimulus at the TM between individuals. Due to the standing wave, the evoking stimulus level at the TM is increased by constructive interference at half-wave resonances, typically at about 8 and 16 kHz, as discussed above for PTA-HTL measurements. Although this will introduce some unwanted inter-subject variability in the stimulus level, it will be partially mitigated by averaging across a one-octave band to obtain the outcome measure of interest in this study (i.e. the band-averaged TEOAE amplitude).

During data collection, SOAEs were measured using the same equipment by recording the microphone signal for 10 sec, with no eliciting stimulus.

5.7 Results

5.7.1 Overview

Test-retest measurements of EHFs (TEOAEs, PTA-HTL, and AFS) were performed for two reasons. First to check the repeatability of the measurement, and second to average the two replicate measurements in order to reduce the impact of extrinsic and intrinsic factors e.g. participant movement and noise in room. To answer the research questions, the results were processed and tested as described in the following sections.

5.7.2 Processing of Results

5.7.2.1 **Amplitudes of EHF PTA-HTL (6-frequency-average) and EHF TEOAE (band average)**

The EHF 6-frequency-average PTA-HTL was calculated as the arithmetic mean of the HTLs expressed in dB HL at the frequencies of 8, 10, 11.2, 12.5, 14 and 16 kHz. The mean (SD) of the 6-frequency-average EHF PTA-HTL was 9.6 dB HL (8.2 dB) across the sample (n=28).

The TEOAE signals were analysed with Matlab by first passing the signal through a bank of eight ½-octave filters spanning the 1–16 kHz range (with centre frequencies from 1.2 to 13.3 kHz). An analysis time window was defined for each band, in which a genuine TEOAE was expected to occur, based on the latency-frequency relationships established in previous studies (e.g. Goodman et al., 2009), as specified in Section 5.2. The window for each band was used for analysing the TEOAE amplitude. The purpose of this time window was to eliminate both potential stimulus artefacts and the sections where noise was expected to predominate. An example of a ½-octave band and the time windows is illustrated in Figure 5.2; the example shows one ear measurement.

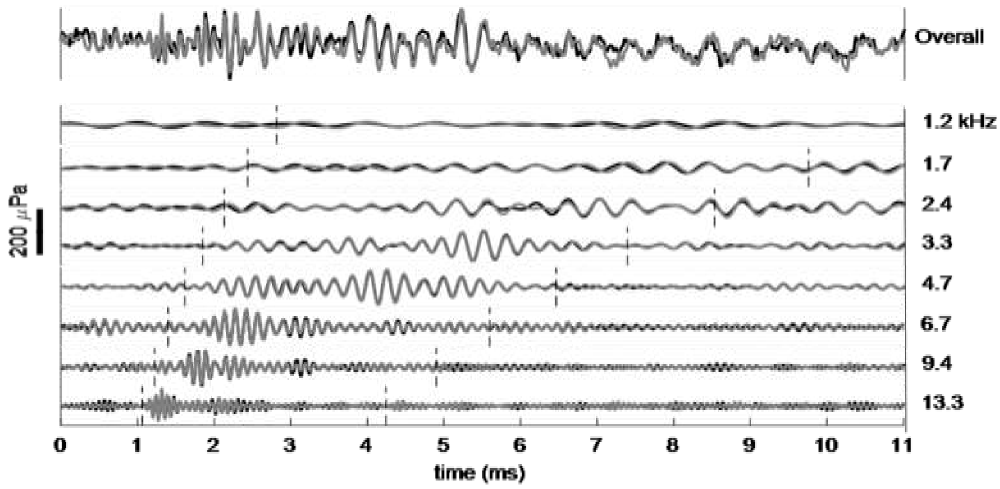


Figure 5.2: Example of TEOAEs measured in one ear using the DE paradigm, evoked using a HPF click of 75 dB peSPL level.Each trace shows two replicates (one black, one grey) overlaid. The top trace shows the overall signal, while the lower eight traces show the output from the ½-octave filter banks, with the centre frequency shown at the right end of each trace. The time-window over which the TEOAE is analysed is shown by vertical dashed lines. A scale bar is shown on the left-hand side as a thick black line.

For each time-window analysis of each ½-octave frequency band, the root mean square (rms) of noise was estimated from the difference between the two replicate waveforms. The TEOAE rms signal amplitude was also estimated using an unbiased estimator based on the mean of the two replicate waveforms, and the previously-estimated noise (e.g. Lineton, 2013). The EHF TEOAE amplitude (8–16 kHz) was estimated by combining the signal power in the two ½-octave frequency bands (those centred on the 9.4 and 13.3 kHz bands). The mean (SD) across the sample (28) of the TEOAE signal amplitude was 6.2 dB SPL (8.0 dB), whereas for the SNR was 5.9 dB (7.8 dB). Calculation of TEOAEs in the ½-octave bands for frequencies below 8 kHz (for the default stimulus) was also performed for descriptive purposes only and did not feature in any further analysis. Box-plots of the PTA-HTLs and TEOAE properties are shown in Figure 5.3. As expected, a statistically significant negative correlation was found between the band-averaged amplitude of the EHF TEOAEs and the 6-frequency-average EHF PTA-HTL (Spearman's rho = -0.49; $p<0.01$).

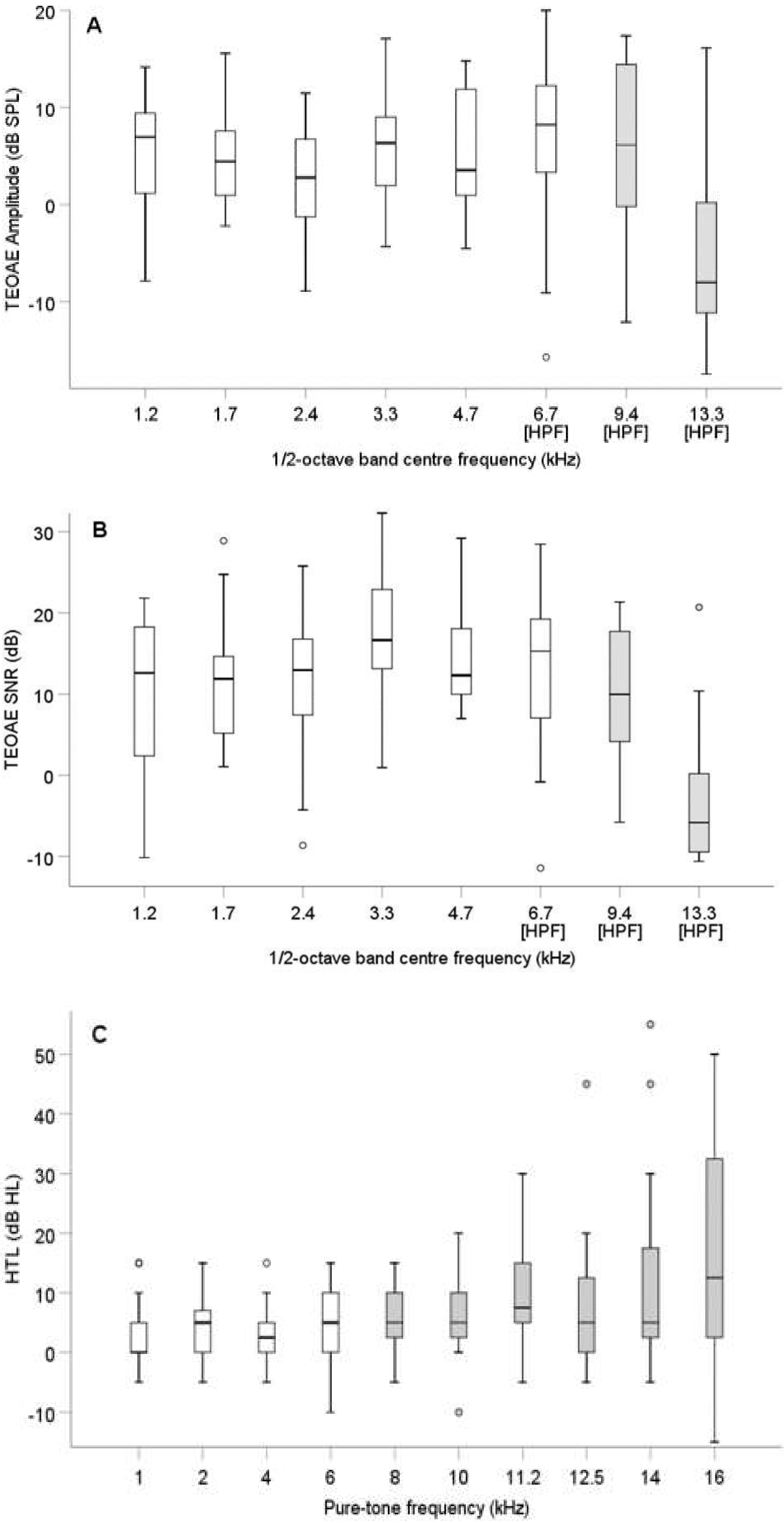


Figure 5.3: Box-and whisker plots for the TEOAEs and HTLs across CAF and EHF- regions.

Boxes represent the interquartile range, with the median shown by a horizontal line. Circles indicate minor outliers, defined using fences 1.5 times the interquartile range. Whiskers represent the maximum and minimum values excluding outliers. Panel A shows TEOAE amplitudes in ½-octave bands. Grey boxplots indicate centre frequencies used in calculating the EHF-TEOAE amplitude (i.e. 9.4 and 13.3 kHz); white boxplots indicate octave bands from 1.2 to 6.7 kHz which are used for descriptive purposes only. The TEOAEs at centre frequencies from 6.7 to 13.3 kHz denoted "HPF" were obtained using the high-pass filtered click stimulus; the other TEOAEs were those obtained using a conventional click stimulus. Panel B shows the SNR of TEOAEs corresponding to the measurements described for Panel A. Panel C shows the HTL at 10 frequencies; the grey boxplots indicate those values used to calculate the 6-frequency average EHF HTL, while the white boxes indicate the HTLs shown for descriptive purposes only.

The box plots in Figure 5.3 illustrate that band-average for EHF TEOAE amplitude is dominated by the single ½-octave band (i.e. 8–11.3 kHz) centred on 9.4 kHz. This was expected for the following reasons: first, as a result of ME transfer function (and possibly also cochlear physiology), the TEOAE amplitudes are known to decrease with increasing frequency of the evoking stimulus. Second, due to the characteristics of the EAC, the calibration method is affected by a half-wave resonance, which will tend to emphasise components around 8 kHz (Charaziak and Shera, 2017). Although these effects are predicted to weaken the sought-after relationship between the AFS and TEOAE amplitudes, they do not tend to invalidate the forthcoming correlational analysis (Section 5.7.4) because the absolute value of the TEOAE signal amplitude is not directly relevant to the study — only the correlation with ripple depth is of interest.

There is another issue related to the SNR of EHF TEOAEs, that it low for a considerable proportion of measurements in the 11.3 to 16 kHz band, thereby making the corresponding estimate of the TEOAE amplitude unreliable. However, this does not invalidate the correlation analysis, nor does it suggest that these individuals should be removed from the analysis. This is because in cases where the true SNR is very low (e.g. ≤ 0 dB) in both of the EHF bands, the unbiased estimate of the TEOAE amplitude will correctly determine that the TEOAE amplitude is low, and is likely to be less than the residual noise floor. In such cases, the unbiased estimate of the rms amplitude (in μPa) tends to be zero. This estimated low TEOAE amplitude still provides the useful information that this individual had TEOAEs that were much lower than the median in the sample. Furthermore, the correlational analysis in Section 5.7.4 used Spearman's rank correlation, which is robust to errors in the absolute values.

5.7.2.2 Audiogram fine structure ripple depth

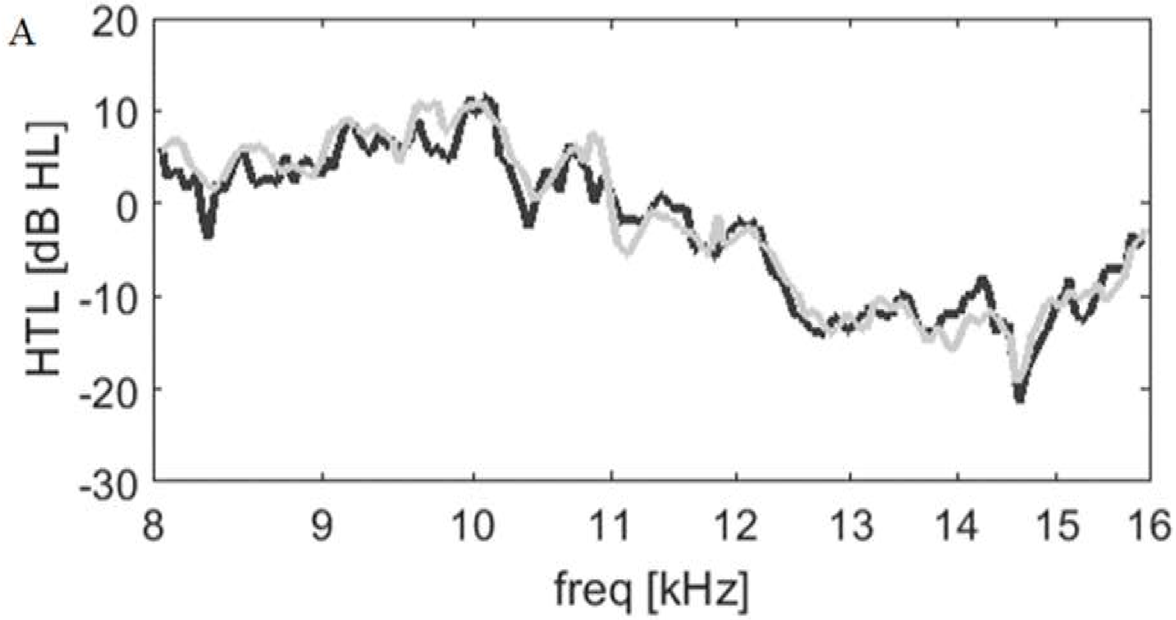
The stimulus levels and resulting HTLs at all frequencies are expressed by dB HL values, which requires estimating the RETSPLs at all frequencies from the published RETSPLs at the seven fixed frequencies in ISO 389-5: (2006), from 8 to 16 kHz. This was achieved by interpolation between the seven fixed frequencies.

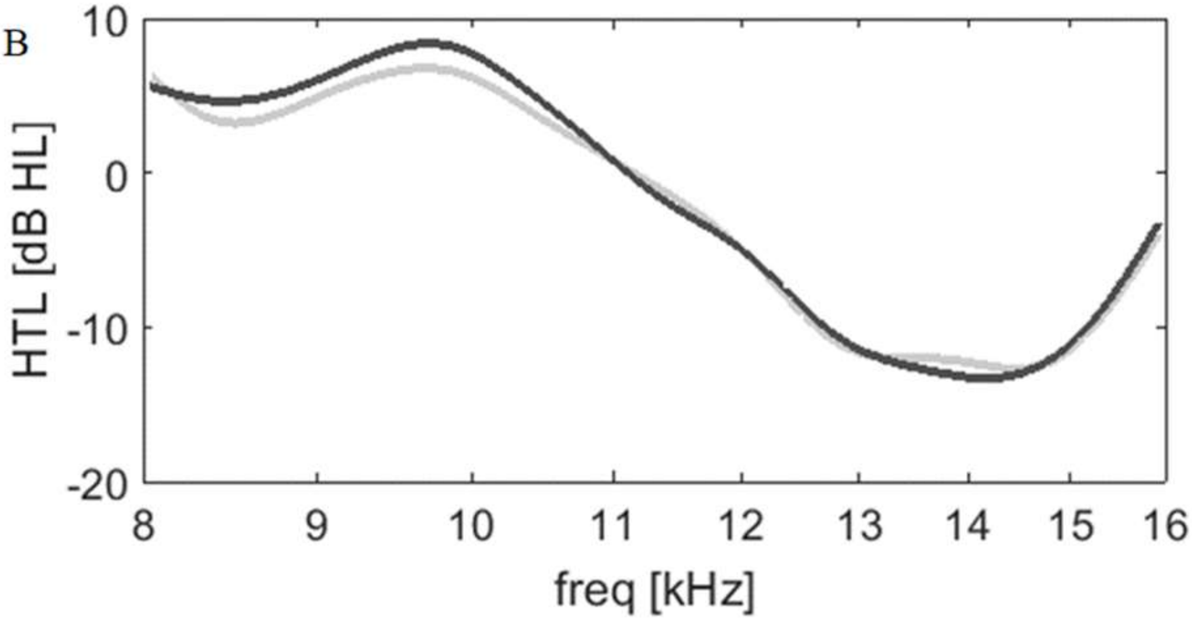
The raw data of Bekesy tracks are sawtooth-shaped waveforms produced by hearing level of the stimulus tone plotted against its frequency, with turning points occurring at each press and release of the response button (alternating direction). Kapadia and Lutman (1999) used an approach that assessed the turning points to remove the features deemed artefactual. Turning-points were classed as “sore thumbs” if they differed by ≥10 dB from both adjacent turning points of the same direction, and pairs of turning points were classified as “glitches” if they were ≤2 dB apart. So, if the turning points fell in any of these situations they were removed. The mid-point between adjacent maxima and minima was defined as the HTL.

To assess the magnitude of spectral periodicity, the HTL trace against frequency was analysed in two ways. The first used identification of peaks in the spectral domain, while the second used a Fourier analysis to transform the audiogram into the “reciprocal spectral periodicity” domain. Further details of the spectral periodicity analysis are illustrated below.

5.7.2.3 Spectral domain analysis of AFS (ripple depth)

The audiogram ripple depth was quantified using a metric derived from the method proposed by Horst et al. (2003). In this current study, HTL-vs-frequency function was first resampled to give equal logarithmic frequency intervals. Then it was separated into two components, based on their spectral periodicity: the audiogram coarse structure and audiogram AFS (Figure 5.4). The coarse structure was obtained using a moving-average spectral filter over a frequency interval of 12.5%, leading to the smoothing out of any spectral ripples that potentially result from standing waves with spacing $fc/\Delta f \geq 8$. Figure 5.4 B shows variations that may arise from phenomena such as EAC acoustic resonance. The component of AFS was then calculated by subtracting the coarse structure from the total HTL-vs-frequency function; this was then used to assess the spectral ripple depth (Figure 5.4 C). The AFS component was then smoothed to remove spectral ripples, which were outside the spectral periodicity range of interest, with spacing $fc/\Delta f \geq 50$.


A
20
10
0
-10
-20
-30
HTL [dB HL]
8
9
10
11
12
13
14
15
16
freq [kHz]


B
10
0
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HTL [dB HL]
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15
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freq [kHz]

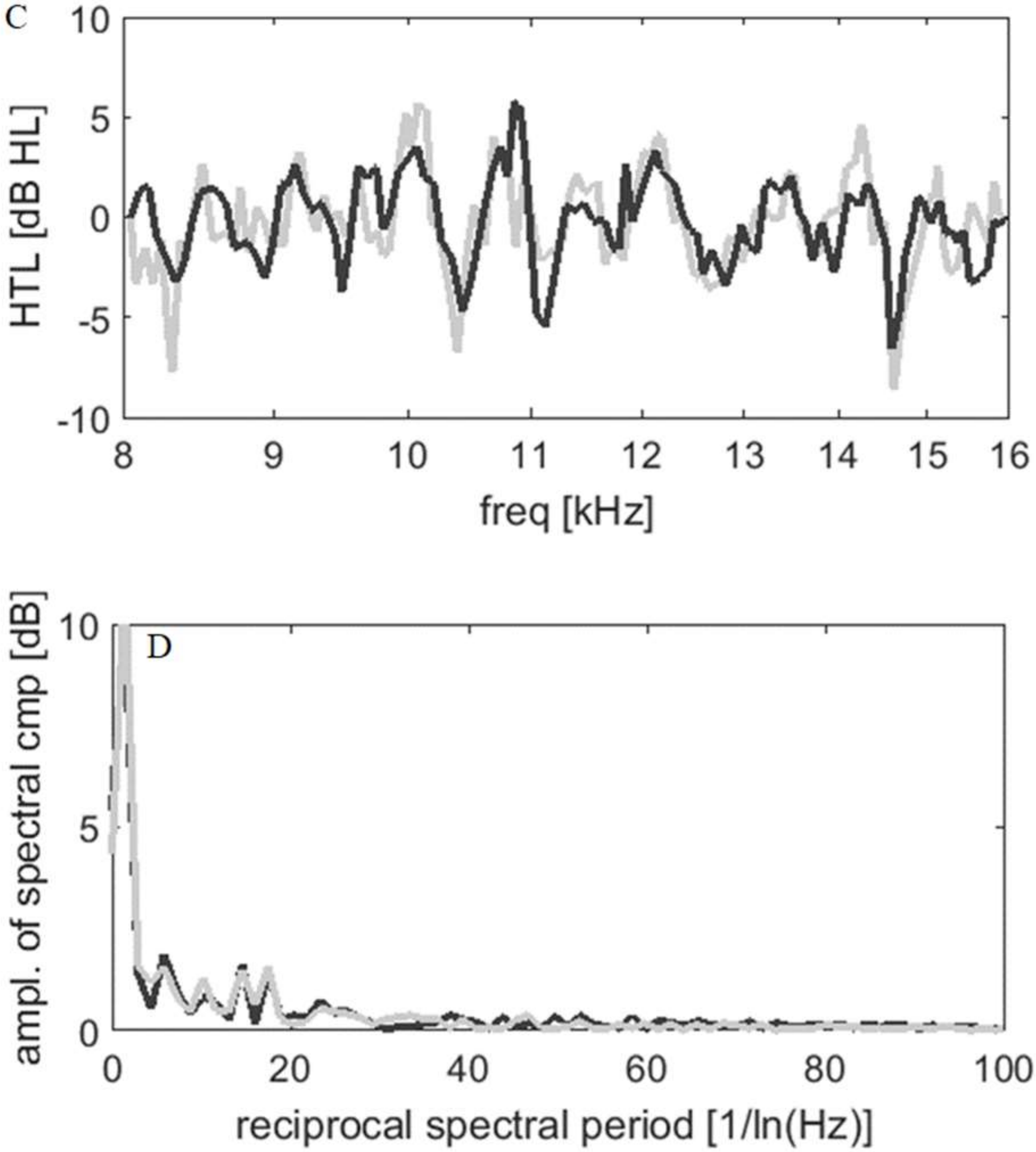

Figure 5.4: Example of two replicates of the Bekesy audiometry track for one participant (grey line: replicate 1; black line: replicate 2).

In Figure 5.4, Panel A illustrates the total HTL-vs-frequency function. Panel B shows the audiogram coarse structure obtained from smoothing the trace in Panel A using a moving-average filter with a frequency interval of 12.5%. Panel C shows the AFS obtained from the difference between the traces in Panels A and B. Panel D shows the reciprocal spectral periodicity distribution which was obtained from the Fourier series coefficients of the total HTL-vs-log frequency in Panel A. The values on the horizontal axis in Panel D are equivalent to values of $fc/\Delta f$.

Correlation between the two replicates was used to assess the test-retest reliability. The median (range) of the correlation for the audiogram coarse and fine structure was 0.97 (0.81–1.0) and 0.6 (0.12–0.79) respectively. The two replicates were then averaged for further analysis.

AFS cycles were identified from adjacent turning points, which were separated by at least 1 dB (Figure 5.5). Each cycle amplitude (dB) was then calculated, and the average across the cycles was calculated as a metric for the mean ripple depth for each AFS.

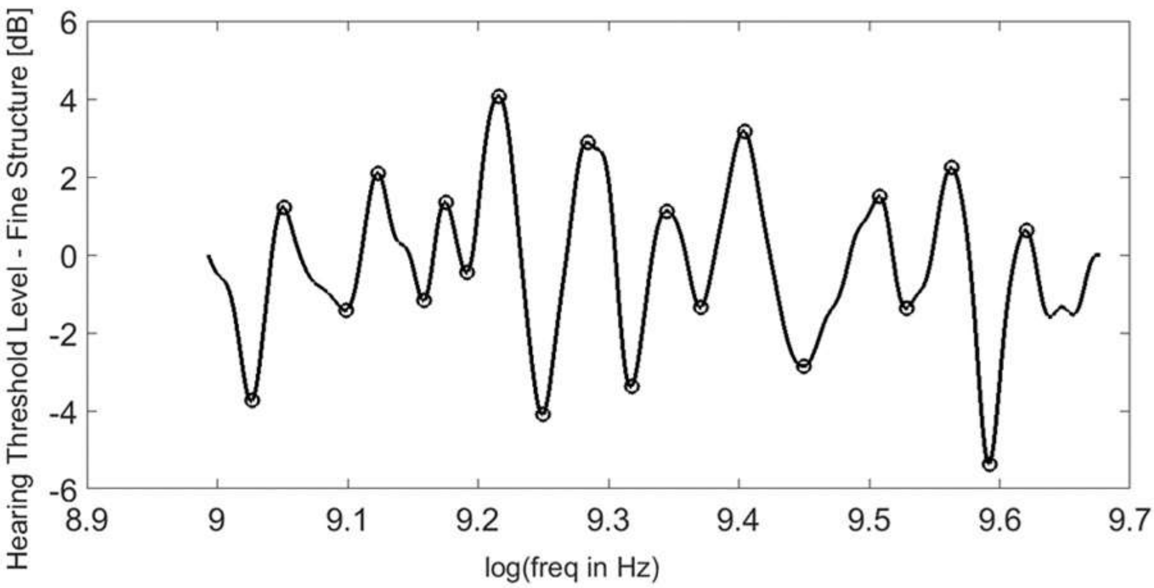

Figure 5.5: An example of the average AFS of the two replicates with turning points extracted.

5.7.3 Reciprocal spectral periodicity domain analysis of AFS (ripple depth)

Another metric was used to quantify ripple depth, following Kapadia and Lutman (1999). The Fourier series coefficients of the HTL-vs-log-frequency function (Figure 5.4 A) were calculated to convert from the log-frequency domain to the "reciprocal spectral periodicity" domain. The distribution resulted is plotted on a horizontal axis with units of $[\ln(Hz)]^{-1}$ (Figure 5.4 D). This unit corresponds to the previously used value of $fc/\Delta f$ (fc is the centre frequency and Δf is the frequency spacing between adjacent ripple peaks). Previous studies report the values of $fc/\Delta f$ to be centred around 15, for CAF (e.g. Kapadia and Lutman, 1999), while other studies based on SOAEs and SFOAEs suggest that the value of $fc/\Delta f$ increases somewhat with increasing fc (e.g. 10 to 20 for values of fc between 0.5 and 8 kHz) (Shera, 2003; Fig. 3). Such features would show as a peak located at a value between 10 and 20 $[\ln(Hz)]^{-1}$ units in the reciprocal spectral periodicity domain.

The average spectral ripple depth was quantified for each subject, from the area under the curve from 10 to 30 $[\ln(\text{Hz})]^{-1}$ in the reciprocal spectral periodicity domain. The range from 10 to 30 was chosen by extrapolating the trend seen in Shera (2003) up to 16 kHz.

5.7.4 Test of relationship between AFS ripple depth, HTLs and TEOAE amplitude

Two hypotheses were tested with both metrics of AFS ripple depth. First, the hypothesis that ripple depth metrics are negatively correlated with the 6-frequency average PTA-HTL, and second that the metrics are positively correlated with the band averaged EHF-TEOAE amplitude. The four Spearman correlation coefficients were conducted for the 28 participants, using a 2-tailed test for statistical significance, without correction for familywise error.

The first hypothesis was rejected, as the AFS ripple depth metric calculated in the spectral domain (as in Horst et al. 2003) was found not to be statistically significantly correlated ($p>0.05$) either with the 6-frequency average PTA-HTL (Spearman's rho = 0.09), or with the band-averaged TEOAE amplitude (Spearman's rho = 0.26).

Likewise, the AFS ripple depth metric calculated in the reciprocal spectral periodicity domain (as in Kapadia and Lutman, 1999) was also found not to be statistically significantly correlated with either the 6-frequency-average HTL or the band-averaged EHF TEOAE amplitude (Spearman's rho = 0.22 and 0.16 respectively).

The two metrics of AFS ripple depth correlated positively with each other (Spearman's rho = 0.73, $p<0.01$), as was expected.

5.7.5 Exploring ripple characteristics of measured AFS

From visual inspection of the AFS, it appears that AFS show weaker and less regular spectral ripples than what was observed in the CAF-ranges. One way of characterising this is to examine the reciprocal spectral periodicity distribution of the AFS. At CAF, Kapadia and Lutman report a distinctive peak in this distribution in the periodicity range of 10 to 20 $\ln[\text{Hz}]^{-1}$ when averaged across those individuals with detectable TEOAEs (Kapadia and Lutman, 1999, Fig. 2).

In order to investigate whether any peak in the reciprocal spectral periodicity distribution was discernible in the EHF AFS data, the average distributions across participants were calculated. The sample was first split into two groups of 14 participants, based on whether the average of EHF-TEOAEs was below or above the sample median. The average distribution across the 14 participants in both groups was then calculated. Unlike what was seen in CAF-range distributions (Kapadia and Lutman, 1999), no discernible peak was visible in either distribution. There was also no clear difference between the two distributions (Figure 5.6).

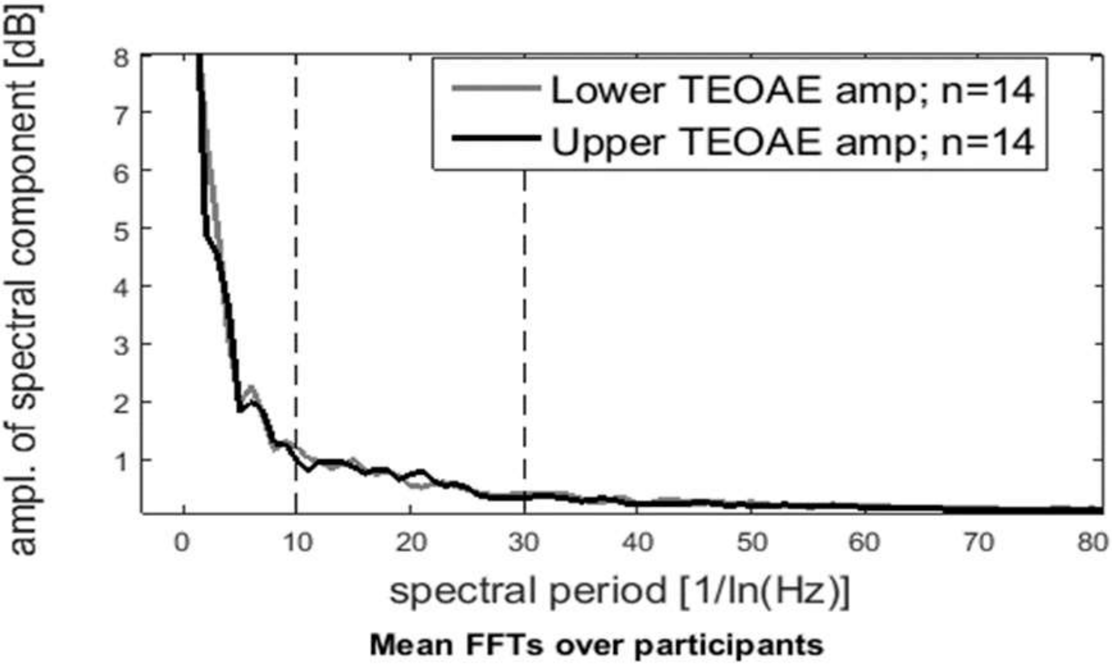

Figure 5.6: The reciprocal spectral periodicity distribution averaged across individuals. Averages from two subgroups of the sample are plotted separately. The grey line is for the subgroup, (n=14) with the highest EHF-TEOAEs averages. The black line is for the subgroup (n=14) with lowest EHF TEOAEs averages

5.7.6 SOAEs

Only a few SOAEs were detected over the frequency range from 8 to 16 kHz, and these had weak amplitudes. With a threshold of 3 dB above the background noise level (estimated from adjacent frequency bins), only four participants exhibited clear SOAEs. Therefore, the SOAEs did not feature in any of the analysis.

5.8 Discussion

5.8.1 Overview

This study aims to establish whether there is a correlation between AFS ripple depth and HTL-PTA and TEOAEs at EHFs, similar to those present in the CAF range. The results of the EHF-region differ from what was reported at CAF in three respects. First, when comparing the EHF-range current result to Kapadia and Lutman's (1999) at the CAF range, no distinctive peak is seen in the reciprocal spectral periodicity distribution in the range of values of fc/Δf from 10 to 30. The current findings also differ from Kapadia and Lutman (1999) in the frequency range from 1.2 to 2.2, where individuals with weak TEOAEs showed weak audiogram ripple. Second, AFS mean ripple depth was lower than has been found in previous studies of CAF, leading to poor test-retest reliability in some ears. That is to say, Kapadia and Lutman (1999) reported ripple depths in the range of 2–12 dB, while Horst et al. (2003) found a ripple depth of about 6 dB (4–10 dB). The present study ripple depth showed a mean of 3.7 dB (1.7–7.1 dB), which is weaker than those of previous studies in the CAF-range. Third, the relationship between ripple depth and both average frequency HTL and TEOAEs showed no significant correlation between the magnitude of AFS ripple depth with either HTLs (frequency-average) or TEOAE amplitude (average frequency-band). This differs from the findings of Horst et. al. (2003) and Kapadia and Lutman (1999) at CAF-range. This non-significance finding differs from findings of Horst et al. (2003; Fig. 3), in that they found a significant correlation between mean ripple depth and the frequency-average PTA-HTL over the range of 0.25 to 3.5 kHz.

5.8.2 Cochlear mechanism for both ripple depth and OAEs

The lack of both amplitude in the reciprocal spectral periodicity distribution and correlation between ripple depth and average frequency band TEOAE amplitude are unexpected from the point of view of predictions made by current theories of cochlear mechanics. The theory proposes that both AFS and TEOAEs arise from both active amplification of the TW and multiple reflections of the TW between apical and basal sites. The reflection from the apical site is thought to be due to inhomogeneities on the basilar membrane near the characteristic place of the stimulus frequency and the reflection from the basal site is due to the stapes (Zweig and Shera, 1995; Talmadge et al, 1998; Wilson, 1980). The theory also predicts that there is a minimum spectral ripple spacing, expected to lead to a peak of the reciprocal spectral periodicity ($fc/\Delta f$) of between 10 and 30 (Zweig and Shera, 1995; Talmadge et al., 1998, Shera, 2003). Support for the applicability of this theory for frequencies up to 13.9 kHz is seen in the relationship between SOAEs and audiogram ripple locations, as reported by Baiduc et al. (2014).

Some possible explanations for the current results were considered in relation to the cochlear mechanical theory outlined above. The weaker audiogram ripple and the lack of any discernible peak in the reciprocal spectral periodicity (Figure 5.4) at EHFs in relation to CAF frequencies might be the result of several causes. The audiogram ripple generation requires several different elements: inhomogeneities along the BM that arise from longitudinal spatial variation in the wave-impedance, coherent reflection of the TW due to the inhomogeneities, active amplification of the travelling wave to give a “tall-and-broad” TW envelope (Zweig and Shera, 1995), and basal reflection from the stapes. Thus, weaker audiogram ripple patterns at EHF-regions may arise from: first, lower gain of cochlear amplifier; second, less potent inhomogeneities; third, a potentially different interaction between the TW and the inhomogeneities; and fourth, differences in cochlear mechanical properties. Shera (2003) suggested that in measurements of SFOAEs, the envelope of the TW becomes increasingly sharply tuned as the frequency of stimulus increases up to 7 kHz, which may be due to increasing cochlear amplifier gain. If this trend continues as frequencies increase (i.e. 8–16 kHz region) then the cochlear amplifier might be expected to show greater gain, and hence a stronger audiogram ripple pattern may also be expected, leading to a greater amplitude in the reciprocal spectral periodicity distribution. However, there is a complication, as increasing the cochlear amplifier gain also leads to a narrower TW envelope, which leads to reflections being less coherent (Zweig and Shera, 1995). Thus, when the TW envelope becomes narrower, any peak in the reciprocal spectral periodicity distribution is expected to become broader, leading to less coherent reflection (Zweig and Shera, 1995). The consequence of this is that the peak in the reciprocal spectral periodicity distribution may become less distinct as it comprises a broader range of spectral periods. A further possibility is that the interference pattern breaks down in the basal cochlear region as the peak in the TW becomes located closer to the stapes, giving a restricted region in which the TW can develop. However, in simulations using a cochlear model incorporating the main elements of cochlear mechanical theory, Ku et al. (2008) predicted cochlear standing waves (which would generate an AFS ripple pattern) in the basal EHF-region, thus suggesting that there is no inherent theoretical barrier to producing AFS ripple in the basal region. The lack of correlation between ripple depth and TEOAE amplitude may also be a type II error arising from both the weaker ripple depth and weaker TEOAE amplitude at EHFs.

5.8.3 Cochlear mechanism for both ripple depth and HTL frequency average

The weaker audiogram ripple pattern described in the previous section can also be one possible reason why the current study found no significant correlation between ripple depth and the frequency-averaged PTA-HTL metrics; the measured ripple depth will be more contaminated by measurement errors in the EHF region than at CAF. Another possible reason that might cause the lack of correlation is that the inter-subject variability in EHF PTA-HTLs is much greater than that at CAF (Bharadwaj et al, 2019; Ahmed et al., 2001; Souza et al., 2014). The higher inter-subject variability is possibly not associated with cochlear activity, but rather might be related to differences in transmission through the OE and ME, which would not affect ripple depth but would rather affect frequency-averaged metrics. Hence, the OE is known to lead to greater inter-subject variability in HTLs, due in part to standing waves in the EAC (Souza et al., 2014). ME transmission function may also lead to greater inter-subject variability, as the transmissibility decreases rapidly with increasing frequency, meaning that small inter-subject differences in the frequency of the “knee-point” in transmission may lead to large inter-subject differences in HTL. If this were the case, then the inter-subject variability due to ME properties would be greater in the EHF region than at CAF. As these additional sources of variability in the frequency-averaged PTA-HTL in the EHF-region are unrelated to the ripple depth, they could explain why any correlation between HTL amplitude and ripple depth is weaker in the EHF-region than the CAF range.

Similar arguments relate to TEOAE amplitudes, which are affected both by forward and reverse transmission through the ME. The measured band-averaged TEOAE amplitude is likely to be dominated by components at the lower end of the frequency range (Figure 5.3 B). The SNR of the EHF-TEOAEs were also reduced at higher frequencies, leading to greater errors in the estimated TEOAE amplitude. Finally, the studies of Kapadia and Lutman (1999) and Horst et al. (2003) both selected participant groups that maximised the correlations seen at CAF, while the current studies relied on inter-subject variability in a sample drawn from a more homogeneous population. In summary, there are several possible reasons for the weaker audiogram ripple pattern and lack of correlations, but no single obvious explanation. The lack of correlation between absolute HTL and ripple depth, as well as the reduced AFS ripple depth at EHFs, will reduce any correlation making it more difficult to detect in this study. Thus, the lack of statistically significant correlation in this study could be a false negative finding (i.e. a type II error). A larger study would be required to assess this.

5.8.4 Limitations

There is a limitation in the current study related to the EHF TEOAE average frequency selection, which means that most of the energy is predominantly in the band with centre frequency 9.4 kHz, while there is dramatically less energy in the band with centre frequency 13.3 kHz (Figure 5.3 B). Thus, the OAE signals are biased toward the lower band octave, as most of the information is from that band (i.e. centred 9.4 kHz). Further research could explore the frequency region between 4 and 10 kHz (for both CAF and EHF), which has not been examined by previous studies (e.g. Kapadia and Lutman, 1999; Horst et al., 2003), as this is where TEOAEs are more readily measured in the EHF region.

In this experiment and experiment 3, data was collected from the same subjects at the same session. Therefore, it would be time-consuming to assess AFS at the CAF range, as the test-retest of AFS at the EHF take about 25 minutes for each subject. Although, including the AFS at the CAF-range might add useful information as it can give an idea of whether subjects with strong AFS at the CAF range has strong AFS at the EHF. Unfortunately, in the current study such measurements were not assessed, as the entire experiment including study 2 and 3 consumed about 1.5 hr and adding the AFS at CAF range would add additional 30 minutes to the experiment duration.

Another issue with measurements in the CAF range is that there is far less variability in the CAF HTLs compared to the EHF HTLs. The main study aims relied on the variability in HTLs to assess the correlation between HTL amplitude and AFS depth.

5.9 Summary of chapter 5

This study aimed to investigate a possible link between spectral periodicity in the audiogram and overall amplitudes of both TEOAEs and HTLs at EHF, as this link has been observed in the CAF range. The hypothesis of this present study was that there is a similar link in the EHF region (8–16 kHz) as for the CAF range. In contrast to findings for the CAF range, no significant correlation was found between the AFS ripple depth and the frequency-averaged amplitudes of either TEOAEs and PTA-HTLs, in the EHF region. Furthermore, this study has demonstrated that AFS ripple depth is weaker in in the EHF region, and that no distinctive peak was noticed in the distribution of spectral periods.

Chapter 6 Study three: Investigating the use of rate-derived non-linear technique for acquiring TEOAEs in the extended high-frequency region

6.1 Overview

This chapter covers study 3 in aiming to establish whether measuring EHF-TEOAEs using the rate-derived non-linear (RDNL) method (which relies on maximum length sequences [MLS]) can elicit better results than the DE method currently used in the study. To cross-check validity, a comparison was made of the OAE signal waveforms of DE and RDNL techniques. The measurement used was first introduced, explained, and discussed. As the data for studies 2 and 3 was collected in the same session from 28 subjects, the EHF-TEOAEs equipment set up resembles that outlined in chapter 5 previously.

6.2 Introduction

TEOAE signals can be contaminated by two components impacting the validity of the recorded OAE. The first is random noise, which is noise from physiological processes such as breathing, blood circulation and postural movements. The second is the stimulus artefact where, together with the genuine OAE, the evoking stimulus from the probe earphone is unavoidably recorded by the probe microphone. Here the contamination of the stimulus may be obvious, especially for the early latency components, < 3 ms (Kemp et al., 1990), where the EHFs OAEs are recorded. Contamination by the stimulus artefact makes it difficult, if not impossible to record a genuine OAE signal in the EHF region without using a derived nonlinear paradigm (e.g., either DE or RDNL techniques) to measure the OAE (section 6.3).

Stimulus paradigms perform differently in their function of reducing the impact of the two contamination factors and improving the SNR (Keefe, 1998; Rasmussen et al., 1998). Each of the paradigms has advantages and disadvantages in terms of how effective they are in reducing both noise and stimulus artefacts. The so-called "linear" paradigm uses a train of uniform click stimuli to reduce noise using conventional synchronous averaging but makes no attempt at all to reduce the stimulus artefact, as it does not separate the linear recording from the nonlinear. This paradigm is hence the most efficient at reducing noise and therefore improving SNR.

Figure 6.1 A shows the stimulus train of the linear paradigm. Although this linear method can be efficient in removing the noise from the measurement, it does not resolve the issue of artefact contamination. Other methods have thus been suggested to eliminate this artefact (section 6.3).

6.3 Stimulus Paradigms for removing stimulus artefacts

To reduce the stimulus artefact, three paradigms have been suggested using nonlinear subtraction. Each one of these paradigms functions in a specific condition, either by manipulating the level or the rate of clicks, such as level derived non-linear method (LDNL) and RDNL method, or by presenting two different stimulus from separate earphones which combine to give a manipulation of the acoustic stimulus level. e.g., DE. These paradigms aim to generate OAE signals which, if genuine, will show a nonlinear response, while the stimulus artefact of probe distortion is most likely to act in a linear manner with regard to the manipulation of the evoking stimulus. The component of the response that grows linearly is then removed, leaving (ideally) only the non-linear component of the genuine OAE. These paradigms are the LDNL, the RDNL and the DE. The stimulus trains are shown in Figure 6.1 B-D.

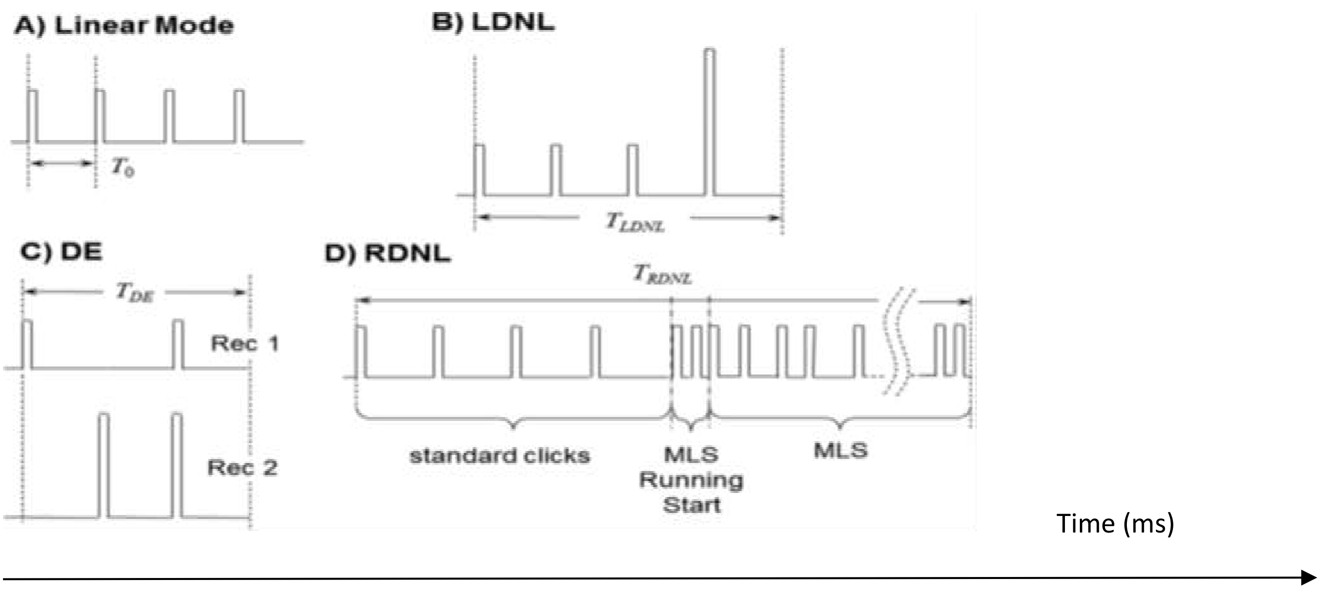

Figure 6.1: examples of four stimulus paradigms used for recording TEOAEs: (A) The linear method in which each epoch is comprised of a single click. Note that a single epoch is defined as the unit that is repeated to allow synchronous averaging. This single epoch is indicated by the vertical dotted line with the double-headed arrow indicating a single epoch's time period. (B) The LDNL method, where each epoch is comprised of a number of standard clicks with equal spacing and similar amplitude, followed by a click with higher amplitude. (C) The DE method, where each epoch is comprised of three clicks from 2 earphones (denoted Rec 1 and Rec 2 for "receiver"): each earphone presents two clicks, only the second of which are synchronous and thus combined, and (D) The RDNL method, where each epoch comprises a number of uniformly spaced standard clicks followed by a MLS 'running start' and one complete MLS.

The figure here is adapted from Lineton (Fig.1, 2013) where the publisher has approved permission to reproduce this figure from JASA (see appendix F).

6.3.1 The LDNL paradigm

This popular version of the LDNL method operates by presenting a train of three clicks followed by a fourth click of a greater amplitude. This method was designed for the original ILO88 and is still used in the Otodynamics equipment for acquiring CAF-OAEs (Kemp et al., 1990). When compared with the linear condition at latencies greater than 6 ms, this technique greatly reduces the linear content of stimulus artefact (Ravazzani et al., 1996). However, compared with the other nonlinear methods, this paradigm has been found to be poor at removing the short-latency stimulus artefact and has not been considered for the current study. The reason for its inadequacy is thought to be its reliance on the earphone which gives the amplitude of the mechanical response as an extremely linear growth in response to a given electrical input.

6.3.2 The DE paradigm

Keefe (1998) developed the DE paradigm to overcome the stimulus artefact at a shorter latency in order to record high-frequency TEOAE. This method is effective because there are two separate earphones, earphone 1 and earphone 2, which each presents a click. The two clicks would combine synchronously in the final third of the epoch to produce a click stimulus of twice the amplitude (Figure 6.1 C). The DE method is similar to the LDNL method in so far as acoustic click stimuli are presented at different levels.

The advantage of the DE method over the LDNL method is that each earphone is driven twice by two electrical pulses which have identical amplitudes in both epochs. Hence the resulting acoustic click components are (approximately) identical, assuming that the earphone has a high acoustical source impedance. This is beneficial because the degree of earphone nonlinearity generally increases as the electrical intensity is increased (requiring greater transducer displacements), leading to a residual stimulus artefact in the derived non-linear waveform. In the DE method then, the increase in acoustic intensity is achieved by having two earphones rather than a greater driving voltage to a single earphone, thus avoiding the increase in stimulus artefact. The change in acoustic amplitude required for the DE to obtain different stimulus conditions is hence achieved by synchronising the two earphones in the last third of the epoch rather than driving either earphone with a greater electrical signal. It should also be noted that some studies have already used the DE method for measuring EHFs-TEOAEs (Goodman et al., 2009).

6.3.3 The RDNL paradigm

The RDNL, which uses a MLS was proposed by Rasmussen et al. (1998), presents a quasi-random train of clicks at a high rate such as that the OAE responses overlap in time. The response is then deconvolved to derive an equivalent response to a single click. The RDNL method hence makes use of two different stimulus rate conditions. First, a low-rate condition similar to the "linear" paradigm (typically 50 clicks/s) and second, a high-rate condition (between 200 and 5000 clicks/s). Like the DE method, the reason why the RDNL method may remove the stimulus artefact more effectively than the LDNL method is that the earphone only presents stimuli at a fixed amplitude and does not rely upon perfect amplitude electromechanical linearity.

The current study aims to determine an improved measurement technique enabling higher frequency components to be recorded. As RDNL and DE are theoretically suggested to be effective in evoking the EHFs signal, they have both been used in this experiment. It is worth mentioning that the RDNL method has been used for longer-latency TEOAE components (Rasmussen et al., 1998; Hine et al., 2001), while also being proposed as a method of obtaining EHF-TEOAEs. However, it has not been used to measure EHF-TEOAEs, nor to compare EHF-TEOAE waveforms directly with those from DE-methods.

6.4 Gaps in the research and motivation for the study

Information on the EHFs region might prove useful in detecting the early sign of hearing changes, even though EHF-TEOAEs are used infrequently for clinical purposes. Using the LDNL paradigm, the clinically applied CAF-TEOAEs typically stops at 4 or 5 kHz in its technique of eliminating the first 3 ms time window, which is usually contaminated with stimulus artefacts. This time interval also contains signals of the EHFs region to be removed with this early latency. However, there is little or no published research examining the use of the RDNL technique on EHF-TEOAEs and comparing it with the DE method. It is important to determine which method can better achieve SNRs, so comparing the waveforms and their results in terms of correlation between the methods and the amplitudes.

6.5 Comparison of the SNR of the DE and RDNL paradigms

6.5.1 Theoretical analysis

The SNR for both DE and RDNL paradigms are poorer than the linear paradigm for a given stimulus intensity and recording time. The theories presented in this section on the SNR of DNL are derived from Lineton (2013). The SNR of any DNL OAE depends on at least two things: the chosen stimulus parameters, and the degree of non-linearity exhibited by the OAE response (as determined by cochlear mechanics).

The first factor arises because two or more conditions must be recorded to obtain a single DNL trace, rather than a single recording for the "linear" condition. The greater the difference in stimulus across the conditions, the greater the non-linear component of the differences in OAE responses across these same conditions. For this reason, the SNR of the DNL waveforms increases with the increase in the stimulus differences across conditions i.e. by increasing the rate of the MLS condition in the RDNL case, or increasing the difference in level of the two earphones in the DE condition (Figure 6.2, upper panel).

The second factor involves the degree of intrinsic non-linearity of the cochlear. Due to the need to extract the non-linear response of the OAE, the derivation of DNL waveform involves adding and/or subtracting the recordings in different stimulus conditions. This leads to a loss of some of the signal energy and therefore reduces the SNR. The degree of nonlinearity of the cochlea plays a major role in SNR, quantified here by the metric "μ", which is the gradient of the I/O function in dB/dB ranging from about 0.3-0.6 dB/dB for OAEs. A value of 1 dB/dB (μ=1) would indicate perfect linear growth (and hence no DNL response at all), while a value of 0 dB/dB (μ=0) would suggest complete independence of the OAE to stimulus amplitude, i.e. "perfect saturation" where the OAE waveform amplitude will remain unchanged when the stimulus level is increased. The greater the non-linearity of the cochlear response (i.e., the lower μ is), the greater the SNR. Figure 6.2 shows how the SNR changes as μ changes for different DNL paradigms.

A theoretical comparison between DE, RDNL and LDNL would thus suggest that the resulting SNR depends on the stimulus parameters. In the case of the DE paradigm, the main parameter is the difference between the click amplitudes produced by two earphones in dB. The RDNL paradigm then involves more parameters with the main one of interest being the MLS click rate, R, which can be converted into an equivalent "dB" value by making some assumptions. Figure 6.2 (upper panel) shows how the SNR increases with the MLS rate in the case of RDNL, but how it also increases with the difference in click amplitude in the case of DE. In both cases, the SNR is shown relative to that achieved by the linear paradigm using the same click amplitude for a cochlear nonlinearity, μ=0.5 dB/dB. A value of μ=0.3-0.5 may be appropriate for conventional TEOAEs, but μ may be higher for higher frequencies.

Figure 6.2 (lower panel) shows how the SNR reduces with an increasing μ, while also demonstrating that RDNL and DE have similar SNRs which depend on the MLS rate and DE level difference. They are then predicted to have similar SNRs for the values used in the current experiment. Unfortunately, the stimulus artefacts detected in the RDNL method (section 6.7.2) limited the MLS rate, R, meaning it was lower than that used in other studies (average click rate of 400 clicks/s instead of 2500 clicks/s). In contrast, the DE level difference is limited by the performance of the two earphones and the comfort of the subject (along with the need to avoid eliciting the acoustic reflex).

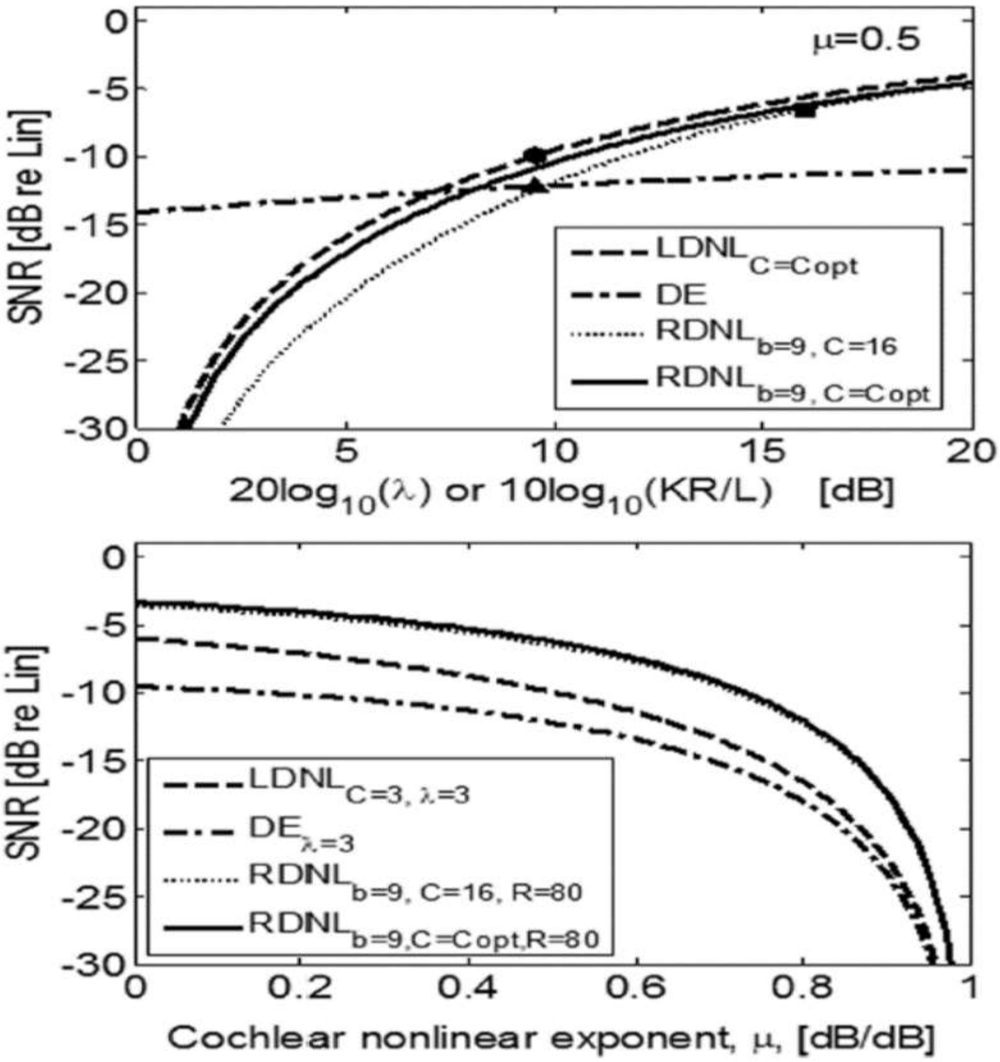

Figure 6.2**:** The lower panel shows how the SNR changes with the changes in μ for different DNL paradigms (with certain assumed stimulus parameters). As μ approaches 1, the SNR approaches minus infinity because the DNL response becomes zero. The figure also shows how the SNR varies with the difference between the two stimulus conditions, expressed in dB. Here SNR increases with MLS rate in the case of RDNL, then increases with the difference in click amplitude in the case of DE. So what this figure shows is that although RDNL and DE have similar SNRs, this depends on the MLS rate and DE level-difference. The other symbols in the figure (K, L, b, and C) relate to other parameters in the MLS that are not so important.

This figure was derived from Lineton (2013). Permission to reproduce this figure was approved by JASA (see appendix F).

6.6 Research questions

RQ.1: Do RDNL and DE paradigms give similar waveforms?

RQ.2: Is the SNR estimated for RDNL better than for the DE paradigm for the same recording time?

6.7 Sample size calculation

Sample size calculation was similar to that conducted for study 3 as data were collected from the same subjects during the same session. In addition, there is a paucity in studies that assessed the EHF-TEOAEs using RDNL and DE therefore making assumptions about sample size and SD might be difficult. Hence, the decision was made to rely on the assumption drawn from horst et al., (2003) that assessed the CAF AFS and HTL.

6.8 Methodology

6.8.1 Practical considerations for the stimulus parameters

For both paradigms, some practical constraints are placed on the choice of the stimulus parameters. For the DE paradigm, for a given click amplitude from earphone 1, the SNR is improved when the click amplitude from earphone 2 is increased as much as possible. This is because any DNL technique using subtraction not only removes the linear stimulus artefact, but also removes part of the genuine OAE, i.e., the part that resembles a "linear" response. The smaller the difference in stimulus level (or stimulus rate) used in the DNL subtraction, the greater the proportion of the OAE signal lost (Lineton, 2013). If the two earphones are driven with the same voltage, then the acoustic click in the final third of the epoch is only 6 dB higher than the clicks in the first two epochs, and hence considerably less than the 9.5 dB difference achieved in the standard LDNL method. However, the maximum click amplitude is limited by the need for the stimulus to be comfortable for the patient, and so avoid eliciting the stapedius reflex. Similarly, for the increase of the RDNL paradigm, the MLS click rate not only leads to an improvement in the SNR but to an increase in acoustic power delivered to the ear. As with the DE paradigm, the MLS rate is limited by the considerations of patient comfort and the need to avoid eliciting the stapedius reflex.

One additional limitation on the RDNL method was found in the current study using the ER-10B+ probe. Here the RDNL method showed unexpected stimulus artefacts (termed here the MLS-artefact) when the MLS rate was set too high. This issue is discussed further in section 6.10.

Both the HPF and the default rectangular click stimuli were used in this study. The HPF is used for stimulating the response for reasons explained previously (see section 3.4.3.1, chapter 3). Prior to data collection, the stimulus artefact was initially investigated by making recordings using the IEC 711 occluded ear simulator with different stimulus parameters. The occurrence of any stimulus artefact was checked for different values of stimulus intensity, MLS rate and stimulus waveform (whether a default uniform click or a HPF).

For the IEC 711 occluded ear simulator, the following maximum MLS rates and DE were found, presented below in Table 6.1. Examples of the recordings in the ear simulator are shown in Figure 6.3,Figure 6.4 and Figure 6.5. Note that the stimulus rates in Table 6.1 and throughout this chapter are the maximum click rates in the MLS (also known as the "click-opportunity rate") which is approximately half the average click rate of the MLS due to the silent intervals within the MLS.

Table 6.1**:** Measurements recorded in the IEC711 occluded ear simulator for RDNL (A) and DE (B) to assess presence of artefacts.

A)

Stimulus waveform	Click amplitude (dBpeSPL)	Stimulus rate (clicks/s)	Comment
Default rectangular pulse	65	2000	
Default rectangular pulse	75	1600	
High-pass filtered pulse	65	1600	
High-pass filtered pulse	75	800	
High-pass filtered pulse	75	3200	Artefacts seen
High-pass filtered pulse	75	4900	Artefacts seen

B)

<table>
<tr><th>Stimulus waveform</th><th>Earphone 1 Click amplitude (dBpeSPL)</th><th>Earphone 2 Click amplitude (dBpeSPL)</th></tr>
<tr><td>Default rectangular pulse</td><td>65</td><td rowspan="4">15 dB above the level of earphone 1.</td></tr>
<tr><td>Default rectangular pulse</td><td>75</td></tr>
<tr><td>High-pass filtered pulse</td><td>65</td></tr>
<tr><td>High-pass filtered pulse</td><td>75</td></tr>
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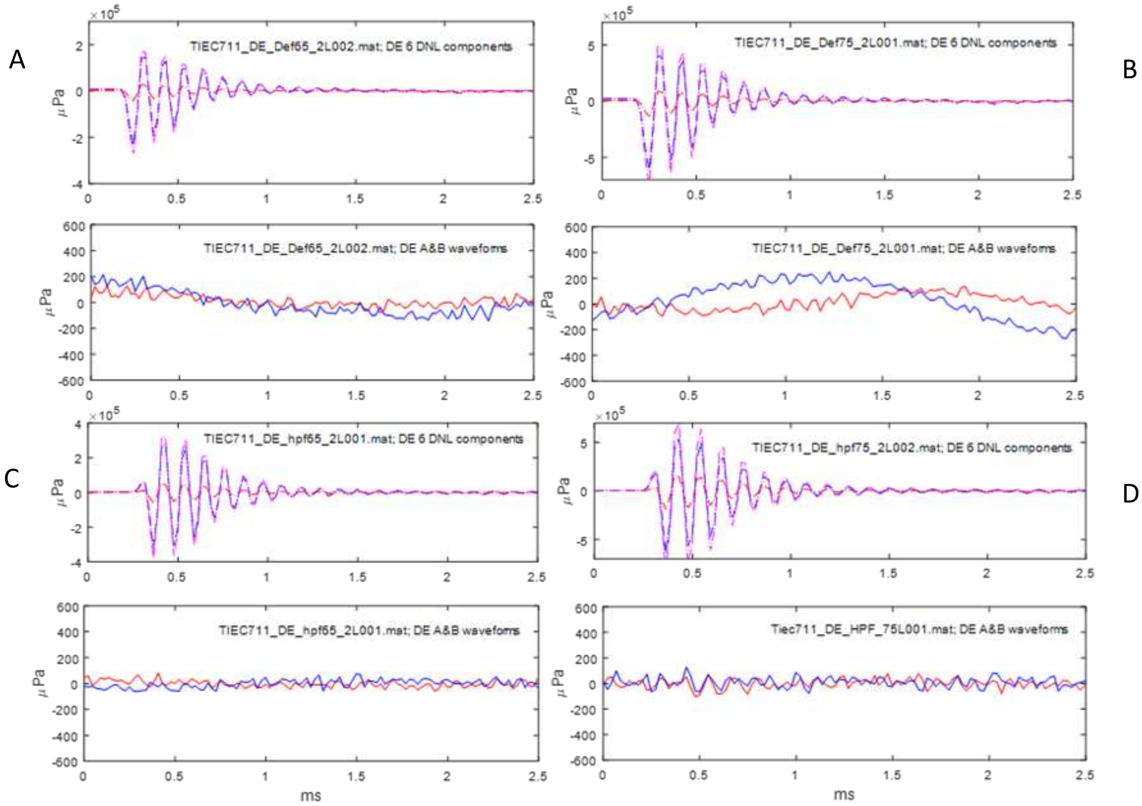


Figure 6.3**:** DE OAEs recording of the IEC 711 occluded ear simulator for 4 stimulus conditions. Two traces are shown for each panel. The upper trace in each panel shows the raw microphone signal which includes the full recording of the stimulus. The lower panel shows the derived non-linear trace which attempts to eliminate the stimulus artefact and is expected to show only residual noise in the ear simulator: (A) default click (earphone1=65/earphone2=80 dB peSPL) (B) default click (earphone1=75/earphone2=90 dB peSPL) (C) HPF (earphone1=65/earphone2=80 dB peSPL) (D) HPF (earphone1=75/earphone2=90 dB peSPL). In each of the panels above, the acoustic default clicks in A and B, while HPF clicks in C and D. The lower panels represent the response on ear simulator with A- and B-replicate stimulus waveforms (red and blue waveforms).

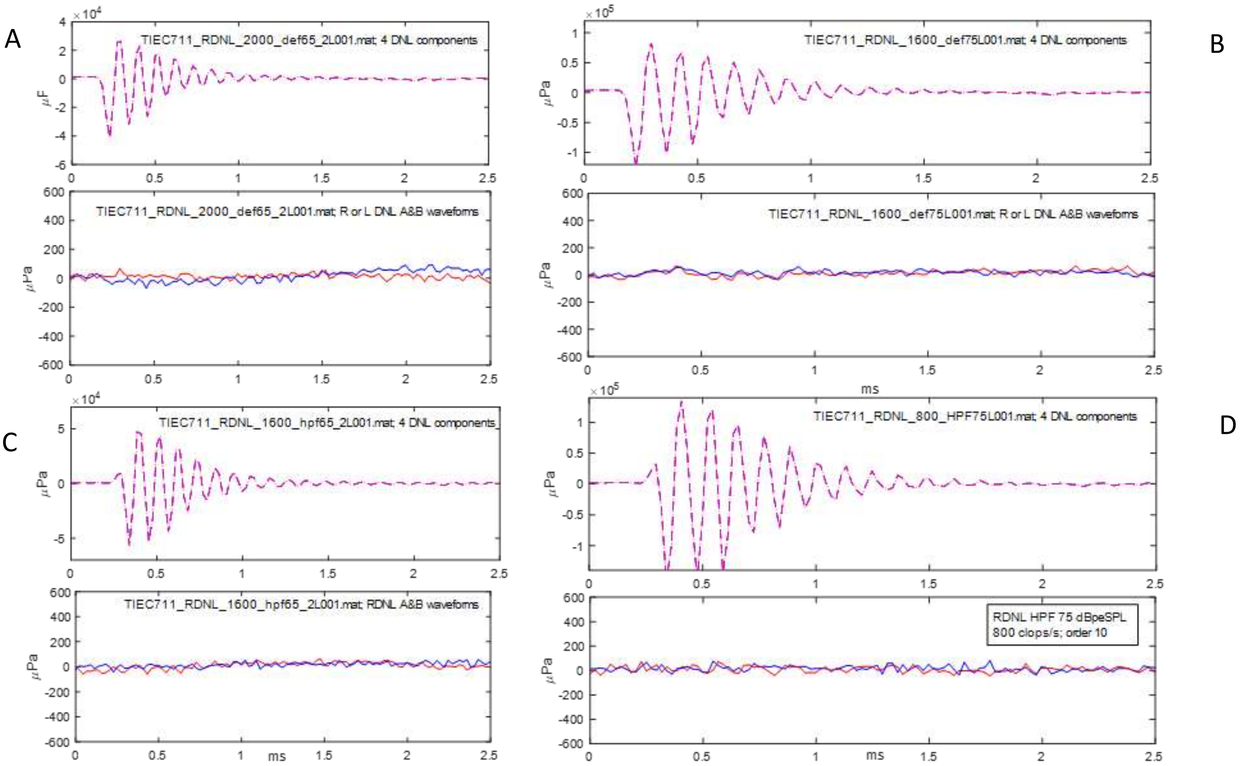


Figure 6.4: RDNL OAEs recording of the IEC 711 occluded ear simulator using different levels and rate presentation. Two traces are shown for each panel. The upper trace in each panel shows the raw microphone signal which includes the full recording of the stimulus. The lower panel shows the derived non-linear trace which attempts to eliminate the stimulus artefact, and is thus expected to show only residual noise in the ear simulator. (A) default click (65dB peSPL/2000 rate) (B) default click (75dB peSPL/1600 rate) (C) HPF (65dB peSPL/1600 rate) (D) HPF (75dB peSPL/800 rate). In each of the panels above, the acoustic default clicks in A and B, while HPF clicks in C and D. The lower panels represent the response on ear simulator with the A- and B-replicate stimulus waveforms (red and blue waveforms).

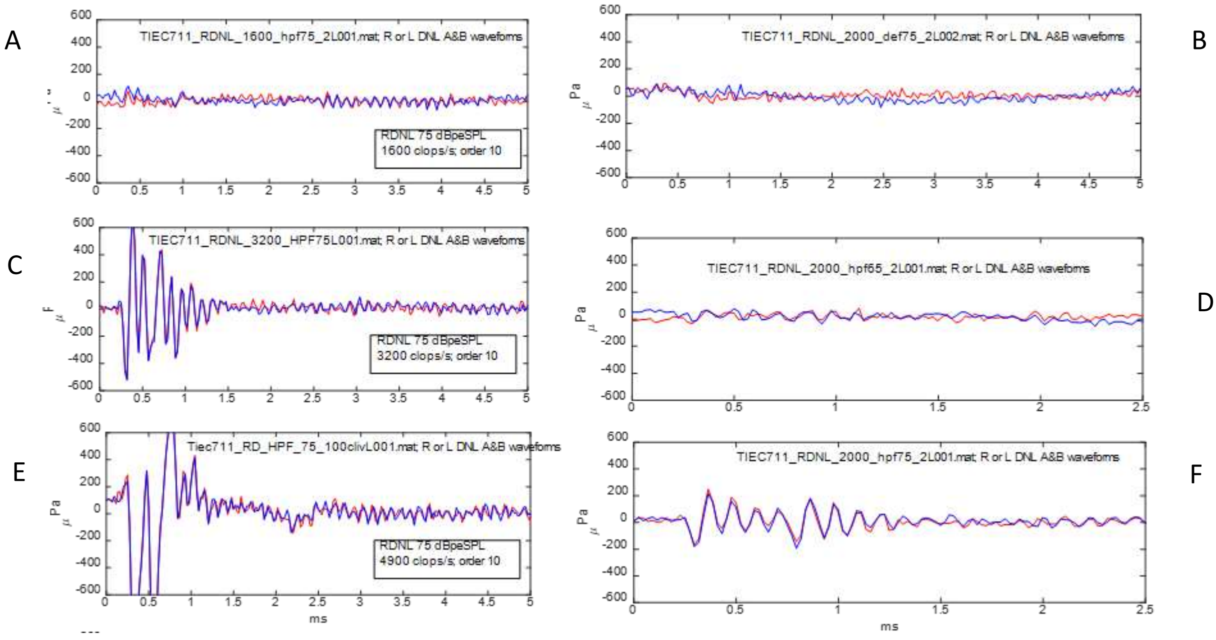


Figure 6.5**:** An example of ear simulator recordings for lower and higher stimulus rates of RDNL OAEs. These are the derived non-linear traces in the ear simulator for which only residual noise is expected to be perceived. They hence give 6 different conditions of clicks level and rate presentation. (A) HPF (75dB peSPL/1600 rate) (B) default click (75dB peSPL/2000 rate) (C) HPF (75dB peSPL/3200 rate) (D) HPF (65dB peSPL/2000 rate) (E) HPF (75dB peSPL/4900 rate) (F) HPF (75dB peSPL/2000 rate). Significant stimulus artefacts are perceptible here which then worsen at a higher MLS rate with higher stimuli, and for HPF rather than the default stimulus.

An inspection of the ear simulator recordings showed that no changes are required for the planned measurement setup at the DE. Correspondingly, no stimulus artefact was indicated. Based on the measurements of the ear simulator, the parameters in Table 6.2 are set for RDNL.

Table 6.2**:** Parameters used for experimental measurements of RDNL

Stimulus filter	Click amplitude (dBpeSPL)	Stimulus rate (clicks/s)
Default rectangular pulse	65	2000
Default rectangular pulse	75	1600
High-pass filtered pulse	65	1600
High-pass filtered pulse	75	800

The presence of significant stimulus artefacts was indicated here. For both higher stimuli and for HPF, these are worse at a higher stimulus presentation rate than for a default stimulus. suspected, the explanation here is that the click-response of the ER10B+ earphones (which have the same design as the ER-2 earphones) shows considerable ringing in the ear simulator as seen in Figure 6.3(A) and 6.4(A) (i.e. top left) for a rectangular electrical voltage input to the earphones. It may be speculated that this ringing leads to the production of the artefacts in the RNDL waveform at high stimulus rates, an issue further discussed in section 6.10.

6.8.2 Experiment apparatus

The experimental equipment used here was the same as that described in chapter 5, section 5.5. In addition, data was collected from the same 28 participants (section 5.5.2)

6.8.3 Stimulus conditions

Both DE and RDNL paradigms were used in the current study with different stimulus levels and waveforms. Table 6.3 shows the stimulus conditions used in term of the rates, the number of repeats, the duration of each recording and the order of presentation.

Table 6.3**:** Summary of the stimulus conditions followed in this study.

Measurement conditions[2]	Stimulus level (dBpeSPL)	Abbreviation [1]
DE-Default rectangular pulse	earphone 1/ earphone 2 (dB peSPL)	Def DE 65
	65/80	
DE-Default rectangular pulse	75/90	Def DE 75
DE-HPF	65/80	HPF DE 65
DE-HPF	75/90	HPF DE 75
RDNL- Default rectangular pulse	Stimulus: level (dB pe SPL)/rate (clicks/sec)	Def RDNL65
	65/2000	
RDNL- Default rectangular pulse	75/1600	Def RDNL 75
RDNL-HPF	65/1600	HPF RDNL 65
RDNL-HPF	75/800	HPF RDNL 75

[1]Note. Throughout this chapter the following abbreviations refers to what condition used for DE and RDNL.
[2]All recordings were performed twice in succession with a duration of 70 sec.

6.9 Results

To answer the question of which paradigm might have better SNR, the results were processed and tested as follows. First, a visual inspection of the waveforms was conducted. Second, measurement was made of the SNR for the DE and RDNL paradigms for band-averaged EHF TEOAEs.

6.9.1 Processing the results

6.9.1.1 Visual inspection of EHFs TEOAE waveforms to compare the DE and RDNL results

Here, analysis was performed to answer the afore-mentioned research questions. The first task was therefore to compare the DE paradigm waveform with the RDNL. This research question was initially evaluated through visual inspection. Figure 6.6 shows that both waveforms are generally similar, as similar morphology was expected of waveforms of similar origin. The difference was that in the HPF case the short-latency components corresponding to EHF are greater in amplitude for the DE paradigm than the RDNL paradigm.

The correlation coefficients between the DE waveform vs. the RDNL waveforms were also calculated by conducting a sample-by-sample Pearson correlation for each pair of waveforms over the recording bandwidth of 0.6 to 16 kHz, after averaging the replicates waveforms. Because these correlation coefficients are affected by residual noise in the recording, they were also assessed in comparison with the correlation between the two interleaved replicates (A- and B-waveforms) for each recording, i.e. waveform A vs. waveform B. These correlations were conducted for the two sequential replicates (denoted replicate 1 and 2) and for both stimulus types (HPF and def). The correlation between A and B waveforms indicates how much noise is likely to be affecting the correlation, and is directly related to the estimated SNR.

For each recording the signal amplitude, SNR and noise were calculated at 9.4 and 13.3 kHz centre frequencies. for a specific time window depending on the octave band (ass in section 5.7.2.1, chapter 5). The two replicates were then averaged across subjects for further analysis. Only the EHF ½ -octave band centred at 9.4 and 13.3 kHz were included in analysis.

The correlation of DE vs. RDNL, showed a positive correlation coefficient between the waveforms, (Table 6.4 B) indicating that the shapes of the waveforms are similar, though not necessarily the amplitudes.

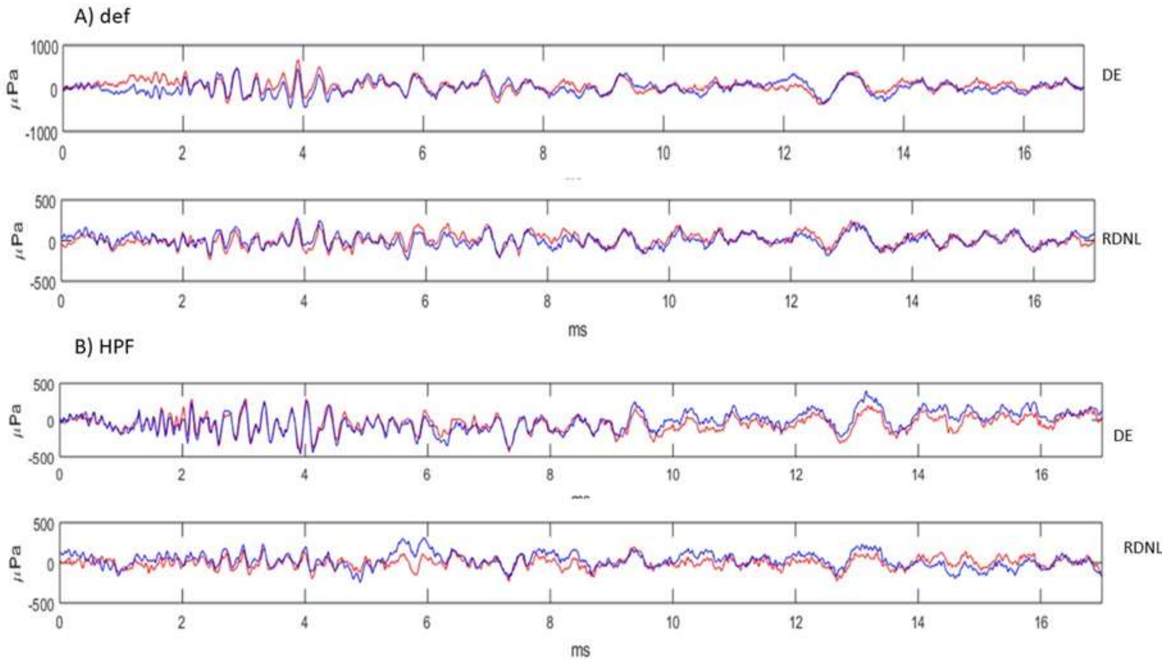


Figure 6.6**:** Example of wave forms for subject 1, illustrating the similarity between RDNL and DE waveform morphology, where the red and blue lines indicate the two replicates (the A and B waveforms). The stimulus level was 75 dB peSPL: A) The default stimulus was above row DE parameter, while the bottom row is RDNL. B) The HPF stimulus was above row DE parameter, while the bottom row is RDNL.

Table 6.4: (A)Median across 28 subjects of the Pearson correlation coefficient between (A) the A- and B- interleaved replicates across the whole-wave recording bandwidth (0.6 to 16 kHz) and (B) between the DE and RDNL waveforms across the whole-wave recording bandwidth (0.6 to 16 kHz).

A)

Stimulus condition	Median correlation coefficient	
	Replicate 1	Replicate 2
Def DE 65	0.52	0.57
Def DE 75	0.75	0.54
HPF DE 65	0.44	0.49
HPF DE 75	0.68	0.63
Def RDNL 65	0.30	0.47
Def RDNL 75	0.77	0.74
HPF RDNL 65	0.33	0.35
HPF RDNL 75	0.48	0.44

B)

Stimulus Level dB peSPL	Stimulus type	Median correlation coefficient
65	Default	0.43
75	Default	0.77
65	HPF	0.42
75	HPF	0.38

The waveform correlations in Table 6.4 A and B depend only on the shape of the waveform over the full recording bandwidth and duration, but independent of the amplitude. To test whether correlation coefficients between the estimated amplitudes of the two stimulus paradigms (DE and RDNL) were calculated for the 9.4 and 13.3 kHz ½-octave bands across the 28 participants (Table 6.5). A high correlation coefficient between the SNRs obtained from the DE and RDNL paradigms indicates that subjects with higher-than-average SNRs for the DE paradigm also show higher than average SNRs for the RDNL paradigm. There are statistically significant correlations between DE results and RDNL results on 5 out of the 8 cases where the SNRs were matched on the remaining measurement parameters (stimulus level, stimulus waveform and ½-octave band frequency) shown in the highlighted diagonal line in Table 6.5. This gives confidence that the DE and RDNL methods of obtaining EHF TEOAEs are measuring similar quantities.

Whether the DE or the RDNL paradigms lead to higher SNRs for the EHF TEOAE is a question that is tested statistically in section 6.9.1.2.

Table 6.5: Correlation coefficients between waveforms of RDNL and DE at the EHFs for HPF and default, for both stimulus level and the two ½-band octaves.

Pearson's correlation	Def DE 65/ 9.4 kHz	Def DE 65/ 13.3 kHz	Def DE 75 / 9.4 kHz	Def DE 75/ 13.3 kHz	HPF DE 65/ 9.4 kHz	HPF DE 65/ 13.3 kHz	HPF DE 75/ 9.4 kHz	HPF DE 75/ 13.3 kHz	Def RDNL 65/ 9.4 kHz	Def RDNL 65/ 13.3 kHz	Def RDNL 75/ 9.4 kHz	Def RDNL 75/ 13.3 kHz	HPF RDNL 65/ 9.4 kHz	HPF RDNL 65/ 13.3 kHz	HPF RDNL 75/ 9.4 kHz	HPF RDNL 75/ 13.3 kHz
Def DE 65 / 9.4 kHz																
Def DE 65/ 13.3 kHz	0.35															
Def DE 75 / 9.4 kHz	0.70**	0.49**														
Def DE 75/ 13.3 kHz	0.53**	0.62**	0.69**													
HPF DE 65/ 9.4 kHz	0.83**	0.41*	0.91**	0.66**												
HPF DE 65/ 13.3 kHz	0.74**	0.38	0.59**	0.61**	0.67**											
HPF DE 75/ 9.4 kHz	0.69**	0.46*	0.84**	0.64**	0.83**	0.65**										
HPF DE 75/ 13.3 kHz	0.57**	0.57**	0.56**	0.75**	0.50**	0.8**	0.62**									
Def RDNL 65/ 9.4 kHz	0.33	0.47*	0.53**	0.78**	0.52**	0.62**	0.48*	0.63**								
Def RDNL 65/ 13.3 kHz	0.21	0.18	0.42*	0.14	0.40	-0.05	0.30	0.09	0.13							
Def RDNL 75/ 9.4 kHz	0.522	0.61**	0.66**	0.72**	0.59**	0.64**	0.64**	0.82**	0.71**	0.24						
Def RDNL 75/ 13.3 kHz	0.62**	0.56**	0.49**	0.50*	0.65**	0.54**	0.36	0.38	0.40*	0.03	0.41*					
HPF RDNL 65/ 9.4 kHz	0.59**	0.42*	0.65**	0.64**	0.69**	0.70**	0.61**	0.68**	0.70**	0.24	0.82**	0.59**				
HPF RDNL 65/ 13.3 kHz	0.60**	0.35	0.40*	0.41*	0.48*	0.51*	0.24	0.42*	0.43*	0.41	0.26	0.53**	0.44*			
HPF RDNL 75/ 9.4 kHz	0.29	0.42*	0.48*	0.68**	0.43*	0.61**	0.41*	0.62**	0.68**	-0.04	0.56**	0.38	0.54**	0.31		
HPF RDNL 75/ 13.3 kHz	0.14	0.60**	0.45*	0.24	0.30	-0.14	0.37	0.16	0.18	0.35	0.31	0.41	0.25	0.15	0.18	

Statistically significantly at 0.01**, statistically significantly at 0.05*

6.9.1.2 Comparing the SNR for the DE and RDNL paradigms for band averaged EHF TEOAEs.

The data for the EHF TEOAEs was calculated from a total of 4 replicate waveforms, comprising of two sequential recordings, each with two interleaved (A and B) replicate waveforms. These were processed using matlab to obtain an estimate of the signal with the best SNR. Two potential sources of noise could then be said to be detrimental to the SNR. The first is direct additive noise, such as acoustical physiological noise radiating from the ear canal walls due to heartbeat, breathing or muscle movements. The second is "drift noise", which can occur owing to slight changes in probe fit or ME properties over the course of the recording. In turn, this may result in the OAE waveforms in successive epochs changing slowly over time which will be interpreted as noise estimated from the difference waveform between replicates.

The interleaved recordings (A and B waveforms) are less susceptible to drift noise than sequential recordings, being obtained from epochs that are very closely spaced in time (typically 20 ms apart). In cases where drift noise is low compared to additive noise, an improved SNR can be obtained by first averaging the two sequential recordings (thereby reducing additive noise) and then estimating the SNR from the resulting A and B waveforms.

The following procedure was then utilised to optimise the SNR involving the calculation of three SNR values. The first value was from the A and B waveforms of the first recording, while the second came from the A and B waveforms of the second recording, and third value came from the A and B waveforms, taking the waveform average of the first and second recordings, which was expected to give the better SNR (ideally by 3 dB) unless the drift noise dominated the additive noise. The best of the three SNR values was then chosen to select the final dataset to be used in the calculation.

For the chosen data set, the signal amplitude, SNR and noise were calculated for the two ½octave bands centre frequencies at 9.4 and 13.3 kHz, using the selected time window that depends on band frequency (as described in section 6.9.1.1). The null hypothesis of the SNR being the same for the DE and RDNL paradigms was then tested statistically. Data analysis was carried out to answer the second research question using IBM SPSS statistical for Windows, Version 25.0 and MATLAB. The SNR data was then collected for the two stimulus waveforms (default rectangular click and HPF) and two stimulus levels (75 and 65 dB peSPL) for the two paradigms (DE and RDNL). For both stimulus levels, the box-plots of the TEOAE SNR results for the default click and HPF stimuli waveform are shown in Figure 6.7. The two ½-octave bands for the EHFs (centred at 9.4

and 13.3 kHz) were shown in Figure 6.7. These two bands are the only bands included in the analysis of EHF-TEOAEs.

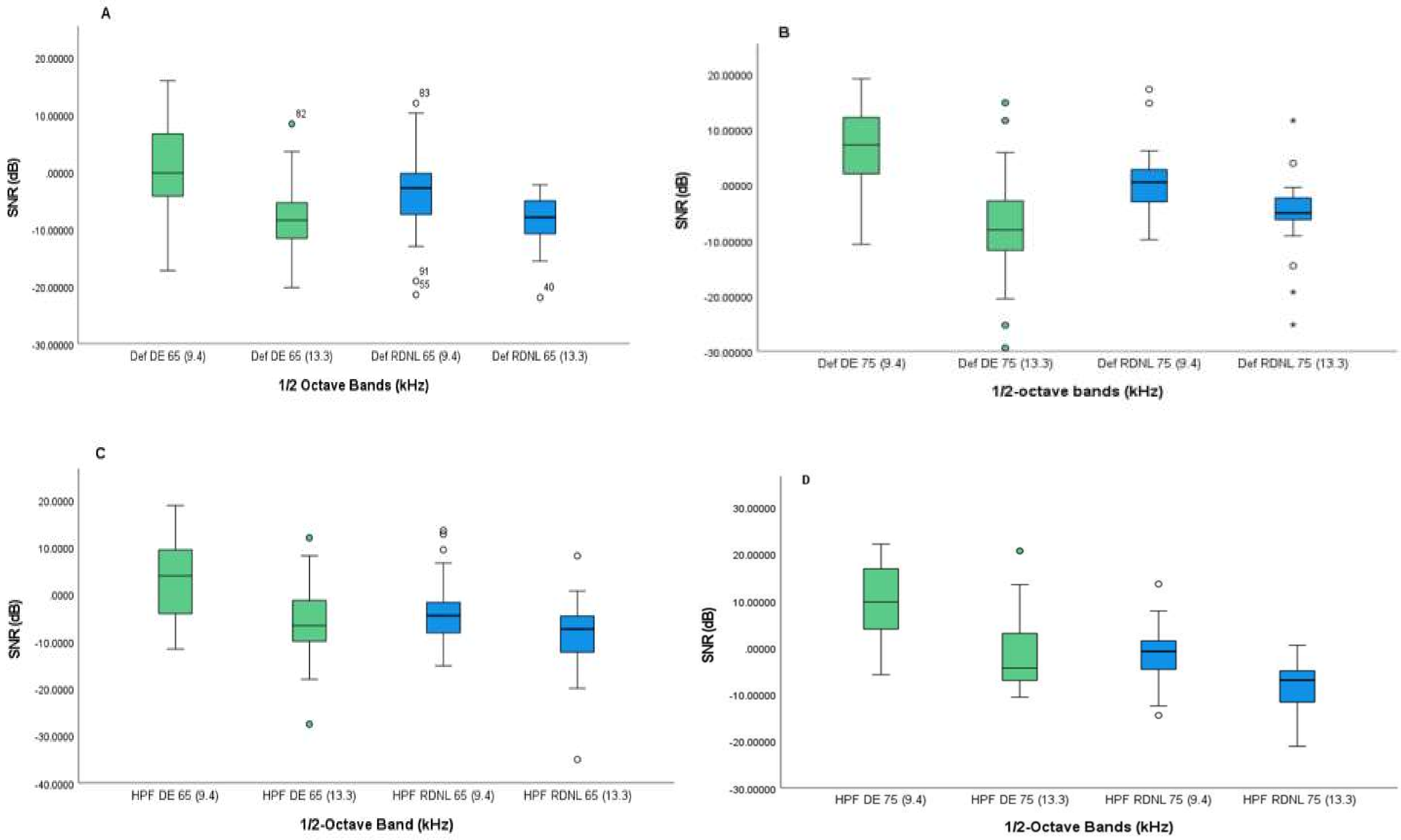

A
SNR (dB)
20.00000
10.00000
.00000
-10.00000
-20.00000
-30.00000
Def DE 65 (9.4)
Def DE 65 (13.3)
Def RDNL 65 (9.4)
Def RDNL 65 (13.3)
1/2 Octave Bands (kHz)
B
SNR (dB)
20.00000
10.00000
.00000
-10.00000
-20.00000
-30.00000
Def DE 75 (9.4)
Def DE 75 (13.3)
Def RDNL 75 (9.4)
Def RDNL 75 (13.3)
1/2-octave bands (kHz)
C
SNR (dB)
20.0000
10.0000
.0000
-10.0000
-20.0000
-30.0000
-40.0000
HPF DE 65 (9.4)
HPF DE 65 (13.3)
HPF RDNL 65 (9.4)
HPF RDNL 65 (13.3)
1/2-Octave Band (kHz)
D
SNR (dB)
30.00000
20.00000
10.00000
.00000
-10.00000
-20.00000
-30.00000
HPF DE 75 (9.4)
HPF DE 75 (13.3)
HPF RDNL 75 (9.4)
HPF RDNL 75 (13.3)
1/2-Octave Bands (kHz)

Figure 6.7**:** Box-and whisker plots of the estimated SNR at 1/2-octave centre frequencies for the TEOAEs recorded with the DE and RNL paradigms with (A and B) default click at 65 and 75dB stimulus level (B and C) HPF at 65 and 75 dB. Boxes represent the interquartile range, with the median shown by a horizontal line. The circles here indicate minor outliers, defined using fences 1.5 times the interquartile range. The whiskers represent the maximum and minimum values excluding outliers. Green boxplots indicate the SNR of DE and the blue boxplots indicate the SNR for RDNL, while the frequencies band shown is centred at 9.4 and 13.3 kHz

To compare SNR between DE and RDNL, a three-way repeated measure ANOVA was conducted with SNR as a dependent variable and then with independent variables of 1) paradigm type (DE and RDNL), 2) ½-octave-bands (9.4 and 13.3 kHz), and 3) stimulus waveforms (default and HPF). Both the low stimulus level (65 dB peSPL) and high stimulus level (75 dB peSPL) were analysed separately.

The main effects of paradigm type, stimulus waveform and octave band were all statistically significant for both stimulus levels. The DE TEOAE SNR is statistically significantly greater than the RDNL TEOAE SNR at both stimulus levels (65 and 75 dB peSPL) (Table 6.6). As anticipated, a statistically significant difference was found between the ½-octave bands where 9.4 kHz measured greater SNRs than 13.3 kHz. A similar finding was also observed in chapters 3 and 5 (see section 5.7.2.1).

The effect of the stimulus waveform (default or HPF) was more complicated. For the 75 dB peSPL, the interaction term between stimulus waveform and paradigm type was statistically significant, arising because the HPF led to an improved SNR for the DE paradigm but a poorer SNR for the RDNL paradigm. This trend can be explained by the RDNL paradigm because the HPF required a reduced MLS rate compared to the default click in order to avoid the stimulus artefacts arising. The post-hoc analysis revealed that the improvement in SNR in the DE paradigm was statistically significant at 75 dB peSPL, which was expected due to the additional stimulus energy in the EHF region. No other interaction terms were statistically significant while for the 65 dB peSPL, the interaction term between stimulus waveform and paradigm type was not statistically significant either.

Table 6.6**:** Illustrates the mean/SD of the estimated SNR for the different conditions, together with the differences in marginal means.

Paradigm	½ octave band kHz	Stimulus Condition	Stimulus level	Mean (SD) (dB)	Difference in SNR between conditions (dB)		
					DE vs. RDNL	HPF vs Default[1]	9.4 vs. 13.3
RDNL	9.4	Default	75 dB peSPL	3.35 (6.58)	5.24*	1.47*	9.20*
	13.3			-2.56 (5.45)			
	9.4	HPF		-1.2 (5.7)			
	13.3			-8.35 (4.86)			
DE	9.4	Default		8.14 (7.55)			
	13.3			-5.21 (10.82)			
	9.4	HPF		9.84 (8.49)			
	13.3			-0.54 (9.1)			
RDNL	9.4	Default	65 dB peSPL	-1.43 (7.84)	4.18*	-0.99 (N/S)	8.28*
	13.3			-8.64 (4.75)			
	9.4	HPF		-1.48 (8.06)			
	13.3			-6.8 (6)			
DE	9.4	Default		3.31 (7.83)			
	13.3			-6.24 (5.84)			
	9.4	HPF		6.11 (7.15)			
	13.3			-4.87 (7.29)			

statistically significantly at 0.05*,0,01 ** and 0.001***
NS = not significant.
Interaction term. [1]

6.9.2 The application of derived non-linear use

It is worth highlighting that to be usable in most clinical applications, the estimated SNR required is ideally ≥ 6 dB (and at least 3 dB). Only the DE technique in the 9.4-kHz ½-octave band meet this criterion. Nonetheless, for the purposes of testing the hypothesis of the average differences between conditions, the data present at estimated SNRs < 3dB can still be used to compare the different measurement conditions.

6.10 Discussion

6.10.1 Overview

Evoking and then detecting genuine TEOAEs from the EHF region can be difficult for several reasons. The main consideration for the recording paradigms of conventional OAE, such as the LDNL technique, is that the residual stimulus artefact actually swamps short-latency TEOAEs even after the application of non-linear subtraction due to inherent non-linearity in the transducers.

Conventionally, for CAF-TEOAEs this issue is solved by time-gating the first 3-ms of the TEOAE waveform and so removing any EHF TEOAE components. Additional problems are the lower stimulus energy presented at high frequencies rather than lower frequencies (Goodman *et al.*, 2009). There are also lower TEOAEs for a given stimulus level might be because the EHF region of the BM may be less active. The reverse transmission of OAEs through the ME may be more attenuated at EHFs than at standard clinical frequencies.

In fact, DE has been developed to overcome the impact of time-gating and the loss of high frequency information. Described by Keefe and Ling (1998) as a non-linear method aiming to reduce contamination by stimulus artefacts at time windows of less than 3 ms, DE enables measurement of the early onset of the response without removing the 2–4 ms latency that contains high frequency information. Through this technique, measurements of high frequencies of more than 5 kHz can be obtained with more reliable results, with the method used in both the cross-sectional and longitudinal study mentioned previously in chapter 3 and 4 in this thesis. The down-side is that the DE technique can lead to poorer TEOAE SNR than the conventional LDNL method for a given recording time. Hence, the aim of the study in this chapter was to investigate whether or not the use of other methods can lead to better SNRs, as a previous study suggested that SNR may be better with RDNL than DE (Lineton et al., 2011;Lineton, 2013).

The use of the RDNL method has thus been conducted to compare its SNR and waveform with the original DE used in the current study. Theoretically, both the DE and RDNL paradigms lead to poorer SNRs than the linear method (Lineton, 2013). The use of a non-linear method requires subtractive operations between more than one condition, thus providing less averaging for the same recording time (Kemp et al., 1990; Tognola et al., 2001). The upshot is that the derived nonlinear waveform contains a summation of the noise in each recording condition, which leads to the waveform having a reduced stimulus artefact but with greater noise.

However, it is also important to note that with more than one condition utilised for adding and/or subtracting the recording, a loss of some of the signal energy occurs which then affects the SNR. According to Lineton (2013) analysis, a decision as to which of the two paradigms is most efficient at improving SNR will depend on various stimulus parameters, the main ones being the stimulus levels and the rate of the MLS used in the RDNL method (Figure 6.2). A second factor affecting the SNR is the inherent non-linear growth of the OAE component, quantified by the I/O gradient in dB/dB denoted μ in Figure 6.2. This growth will vary depending on the stimulus frequency and the individual properties of the subject’s cochlea.

For the DE paradigm, there are two main parameters: the two earphone click amplitudes, while in the case of the RDNL paradigm there are five parameters, with the main ones of interest being the rate of the MLS, and the click amplitudes. To compare the two paradigms, it is assumed here that the MLS click amplitude is set to the same level as the lower of the two DE earphone amplitudes leading to reduced peak voltages in the earphones and (somewhat) in microphones (so reducing non-linear transducer problems).

6.10.2 Stimulus artefacts: The ear simulator

In the preliminary study measurement made in the occluded ear simulator (IEC 711) for the ER10B+ probe, large artefacts occurred when using high MLS stimulus rates. It was speculated that the cause of these artefacts was the occurrence of interactions between electromechanical responses to adjacent clicks in the earphone when using this type of probe at a high MLS rate. If the MLS rate is too high, then the mechanical response of the earphone diaphragm to one click may begin to overlap with the response to the following click, leading to greater diaphragm displacements occurring than at lower rates. The overall consequence to a non-linear electromechanical response in the transducers, manifesting itself as unwanted stimulus artefact. So far, this affect has not shown up in previous studies of the RDNL technique which have used different ear-phones (either for the ILO probe or the POEMs probe) (Lineton et al., 2011).

The ER10B+ uses ER-2 receivers offering a wider stimulus frequency band than other receivers to deliver stimulus energy up to 16 kHz. However, their response to a standard rectangular electrical pulse shows a high degree of “ringing”, as seen in Fig. 6.4 A to D. This ringing indicates that the mechanical response to one click overlaps with the response to a subsequent click, potentially leading to non-linear artefactual responses that contaminate the final waveform. This phenomenon may explain why this high-rate artefact was not seen in previous studies featuring different probes with less ringing where the MLS rate was increased to 5000 click/s.

The use of the HPF stimulus further adds to the duration of the electrical driving signal, which in the case of the RDNL paradigm may lead to non-linear transducer interactions at a lower MLS rate. These artefacts appear to have restricted the maximum MLS rates that could be achieved in the RDNL level which reduces the gains predicted in SNR. The reduction in rate was greater in the case of the HPF stimulus compared to the default click. Nevertheless, being that it was uncertain in practice as to what the non-linear OAEs parameter, μ, would be within the EHF range, it was decided best to proceed with assessment of the SNRs for the two paradigms within a sample of real ears.

6.10.3 EHF-TEOAE DE vs. RDNL waveforms

A visual comparison was conducted to answer RQ.1, presented in section 6.6. The findings indicated that the OAE waveform morphology from the DE and RDNL paradigms were similar. Although the waveforms appear similar, greater TEOAE amplitudes were present in the shorter time window for the DE than for the RDNL paradigm, suggesting that DE showed more energy at the EHF-TEOAEs than the RDNL. This finding contradicts Lineton (2013) analysis predicting that RDNL paradigm becomes more effective than the DE paradigm at improving SNR. The MLS rate was greater than the conventional click presentation rate by about 16 times, or about 800 clicks/s, for a conventional rate of 50 clicks/s (see Fig 6.2).

The median correlation between the waveforms replicate for each run was positive for the two octave bands, while being greater for the 75 dB peSPL than 65 dB peSPL. The findings here show that both runs were fairly repeatable within subjects. A comparison between the TEOAE SNRs for DE and RDNL paradigms (RQ.2) was made using 3-way RM ANOVAs with the following factors: paradigm type, stimulus waveform (HPF and default click), and ½-octave measurement band. These tests were conducted separately for the 65 and 75 dB peSPL stimulus levels. The SNR achieved by the RDNL paradigm was significantly poorer than that of the DE paradigm for 65 and 75 dB peSPL (a difference of 4.18 and 5.24 dB respectively), which may in part be explained by the limitations placed on the MLS rate by the need to avoid stimulus artefacts.

It was also found that the TEOAE SNR was higher in the 9.4 kHz band than in the 13.3 kHz band. This result was anticipated from previous findings and may be the result either of the ME transfer function (Puria, 2003) or from cochlear effects. Another explanation might be centre upon the EAC characteristics, where the calibration method is affected by a half-wave resonance which will tend to emphasise components around 8 kHz (Charaziak and Shera, 2017).

For the stimulus waveform, as expected, the HPF led to a greater SNR than the default click stimulus for the DE paradigm in all conditions. This was not the case for the RDNL paradigm at 75 dBpeSPL which may be explained by the fact that, at this stimulus level, the HPF stimulus required a lower MLS rate than the default click in order to avoid stimulus artefacts, leading to a reduced SNR for the same recording time (Table 6.2). These findings clearly show that the DE paradigm leads to a better SNR than the RDNL paradigm for the ER10B (Etymotic) probe.

6.10.4 Limitations

The current study has clear limitations in relation to RDNL. The dispersion of the default rectangular pulse clicks in the RDNL recordings showed some degree of ringing in the ear simulator (Figure 6.4). The clicks in the electrical signal were then shown as pulses, but when converted to an acoustic signal they appeared as ringing within the waveform. This finding might be explained by the failure of the RDNL to show the same results as DE. In other words, owing to the nature of MLS a click might interfere with the next click and where, in this case, ringing might also interfere. One suggestion to eliminate this issue is the use of inverse filtering which filters the earphone driving voltage by presenting the opposite in an attempt to undo the ringing so showing an acoustic signal reaching the eardrum as a pulse. However, this process presents difficulty as it only works if the ear canal of the individual matches those of the ear simulator that was used to design the inverse filter. Conversion of the ringing in the coupler is not necessarily similar in individuals' ears or between subjects. In addition, it might not work for HPF which requires filtering to boost the high-frequency, and where the interaction between signals cannot be stopped.

6.11 Summary of chapter 6

EHF-TEOAE signals were able to be collected with DE and RDNL EHF TEOAEs. The similarity between the waveform of both paradigms suggests that the signals evoked from that region are genuine. The conclusion reached was that the TEOAE SNR obtained using the DE paradigm had greater statistical significance than that obtained using the RDNL paradigm for stimulus levels of 65 and 75 dB peSPL using the HPF-stimulus. These findings allow the assumption that using DE paradigm in the main experiment (chapter 3 and 4) presents more advantages in inducing EHF signal than the application of the RDNL stimulus. In contrast, only the DE technique in the 9.4-kHz ½-octave band achieved an SNR that would be clinically useful (> 6 dB SNR).

Chapter 7 Conclusions, Limitations, Future Work and Clinical Implications

7.1 Summary and Conclusions

Three studies have been presented in this research project exploring two main topics. The first topic assesses the impact of noise exposure on EHF-HTL and EHF-OAEs (study 1A: cross-sectional and study 1B: longitudinal). The second topic investigates EHF measurements (study 2 and study 3). Corresponding conclusions are presented here for each study.

7.1.1 Study 1A: Cross-sectional

This first study set out to determine the association between noise exposure on CAF and EHF hearing function measured with HTL, TEOAEs and DPOAEs. It was also designed to determine which measurement parameters will evoke greater signal amplitudes and SNRs, either for EHF-EOAEs or EHF-DPOAEs. Finally, the correlation of OAE measures with EHF-HTLs were assessed, and then the OAEs most strongly correlated with EHF-HTL were determined.

In a planned LMM analysis, it was found that age did not significantly affect the measurements of hearing, although these results might be partly related to the small age range of the sample. In fact, the NESI scores were shown to be associated with HTL, so having more significance for the EHF-HTL. In contrast, the results of a between-group comparison analysis were inconsistent with those of the LMM analysis. One possible explanation for this inconsistency was the distribution of NESI scores showed a wide variation in high- NESI group NESI scores, which was positively skewed showing a high proportion of relatively low NESI scores.

An rough estimation of NIPTS from the NESI score from ISO 1999 then became possible because this estimate uses the level of noise exposure in dB SPL and the duration of exposure, which comes to form the NESI score because it looks at each of them separately i.e., it estimates the activity's SPL and duration. Compared with the CAF-HTL NIPTS predicted from ISO 1999, the NIPTS in this study was lower than predicted. This finding might be connected to the drawback of quantifying noise exposure with self-reported measurements because subjects could easily overestimate their noise involvement activities, and by the study inclusion criteria.

The second aim of this study was then to determine the impact of the NESI score on DPOAEs and TEOAEs. The pattern was complex overall in the LMM analysis both CAF and EHF-OAE measures were associated with NESI scores, though EHF-OAEs were not in general more strongly affected by NESI scores than were CAF-OAEs.

The subsequent findings were that the (70/70) stimulus level paradigm had the potential to evoke greater EHF-DPOAE amplitudes and SNRs than the (65/55) stimulus paradigm. Using HPF to modify the click stimulus then led to higher EHF TEOAE amplitudes and SNR than the TB (10 kHz), although the main effect was insignificant. Here it is worth mentioning that the (70/70) stimulus was greater for improving the evoked EHF-DPOAEs amplitude and SNR, although it was not better at predicting HTL.

This study also assessed the correlation between EHF-HTL and EHF-OAEs to reveal there to be, as anticipated, a negative correlation between them. As previously mentioned in this analysis, the (70/70) stimulus evoked greater DPOAE amplitudes and SNRs while the (65/55) stimulus was significantly more strongly correlated to EHF-HTLs for both amplitude and SNR. These results imply that the (65/55) stimulus may be better positioned to predict EHF-HTLs than the evoked EHF-DPOAES using the (70/70) paradigm.

In terms of the EHF-DPOAE measurements then, although the (70/70) paradigm evoked DPOAEs with greater SNRs, the (65/55) paradigm appeared to predict EHF-HTLs more strongly. The outcome of these findings is that the (70/70) paradigm might be more useful for monitoring changes in a cochlear function in an individual ear over time, though this hypothesis was not tested in this study. At the same time, the (65/55) paradigm might be more useful for assessing the cochlear function at a single point in time.

Moving on, EHF-DPOAEs and EHF-TEOAEs were both significantly correlated with EHF-HTLs with correlation coefficients that did not differ significantly in size. The study concluded here that EHF-HTL was more closely associated with noise exposure than CAF-HTL. In addition, noise exposure was associated with CAF-TEOAEs and CAF-DPOAEs while a decrease in amplitude and SNR was also observed to be similar to that occurring with an increase in noise exposure.

7.1.2 Study 1B: Longitudinal

The longitudinal section of the first study aimed to assess changes in HTL and OAEs at both CAF- and EHF-range over a two-time interval (up to 8 months and 16 months). An additional objective here was to determine whether or not changes in the amplitude of EHF-OAE predict changes in EHF-HTL, where a statistically significant effect was found on CAF and EHF-HTL over a period of 16 months due to age and noise exposure.

When related to noise exposure, a statistically significant effect was experienced by EHF for the same period, but no significant changes in EHF were observed in relation to aging. Moving contrary to anticipation in the opposite direction, these unexpected trends of change for CAF-HTL relating to age, and EHF-HTL relating to noise exposure, might be a result of unstable calibration.

This study also reported changes in the NESI score associated with changes in EHF-HTL over a period of 16 months. Here the results showed no significant change in TEOAEs and DPOAEs either for CAF and EHF in relation neither to age nor noise exposure. Moreover, there was no correlation between EHF-HTL and EHF-OAE, although there was a positive correlation of EHF-TEOAEs amplitude and EHF-DPOAEs.

7.1.3 Study 2

This study was designed to determine whether or not there is a link between spectral periodicity in the audiogram fine structure and the overall amplitudes of both TEOAEs and PTA-HTLs at EHF as seen in the CAF range. A secondary aim here was to assess whether or not the AFS ripple in the EHF range shows similar properties to that of the CAF-range.

The findings of this study showed no correlation between the AFS ripple depth and amplitudes of TEOAEs and PTA-HTLs at the EHF range. The results also demonstrated that AFS ripple depth is weaker in the EHF range and that no distinctive peak was noticed in the distribution of spectral periods. This may indicate qualitative differences in cochlear function between EHF- and CAF-regions, or it may be a consequence of methodological difficulties in measuring EHF-TEOAEs

7.1.4 Study 3

This study sought to investigate the RDNL and DE stimulus paradigms for evoking EHF TEOAEs. One objective was to assess whether the TEOAE waveforms evoked by the two paradigms were similar in shape. A second goal was to assess whether the DE or the RDNL could evoke TEOAEs with greater SNRs. The findings showed that EHF TEOAE signals could be collected with DE and RDNL EHF TEOAEs.

The similarity between the DE and RDNL full waveform suggests that the signals evoked from that region are genuine. A positive correlation was also found between DE and RDNL TEOAEs. The results concluded that the TEOAE SNR obtained using the DE paradigm was significantly statistically superior to that obtained using the RDNL paradigm for stimulus levels of 65 and 75 dB peSPL using the HPF-stimulus.

This finding would suggest that using the DE paradigm in study 1 has more advantages for inducing an EHF signal than the RDNL stimulus. It was hence concluded that the RDNL and DE wave forms are correlated, but they vary in terms of evoking SNR because DE has greater evoked SNR than RDNL.

In fact, only the DE technique in the 9.4-kHz ½-octave band achieved an SNR that would be clinically useful (> 6 dB SNR). Moreover, the RDNL paradigm could not be used with the ER-2 earphones and with the HPF stimulus waveform at very high stimulus rates (> 800 click/s) due to the generation of stimulus artefacts. These constraints may have limited the SNR achievable with this paradigm.

7.2 Final discussion

The ultimate aim of the current research was to better understand the EHF- hearing function in terms of providing information on the long-term impacts of noise exposure on young adult EHF hearing function and both EHF hearing physiology and measurements. The study's first aim was to assess the effect of relatively low levels of mostly recreational noise exposure on HTLs, TEOAEs and DPOAE both in CAF and EHF-ranges. The second aim was to identify a better way to evoke EHF-TEOAEs in terms of signal amplitude and SNR in normal CAF-HTL ears. The third aim was to understand whether the cochlear physiology for HTL and OAE at EHF is similar to that found in the CAF range.

7.2.1 Noise exposure and EHF hearing measures

Previous findings have suggested that noise exposure is associated with elevated HTL at the EHFs (Ahmed et al., 2001). There are few studies that looked at the impact of noise exposure on EHF-OAEs. Therefore, this has generated interest in investigating whether EHF-OAE measurements can show a similar association with noise exposure and which EHF-OAE measurements can evoke greater SNR. We also investigated which is most appropriate to predict HTLs within an noise-exposed young adult population.

From these findings, it was determined that the NESI scores were shown to be associated with EHF-HTL more than the CAF range from cross-sectional data. On the other hand, TEOAEs and DPOAEs at the EHFs did not show similar findings, as both CAF and EHF ranges were associated with noise exposure at a similar level.

One possible explanation for why there was no statistically significant correlation between NESI score and EHF-DPOAEs and EHF-TEOAEs, is that the standing wave in the ear canal tends to emphasise or de-emphasise the EHF component depending on the individual's ear canal, which leads to increased inter-subject variability. Another reason relates to the ME transmission function that does not adequately transmit the EHF signal from and to the cochlea. This can lead to the insufficient recording of the EHF-DPOAE amplitude, and therefore no association would be reported. Not seeing a similar effect of noise exposure on EHF-OAEs, as was found with EHF-HTL, might be due to the ear canal resonant frequency characteristic which in the EHF-OAEs do not affect the inward signal as HTL but are also impacted by the outward signal (Charaziak and Shera, 2017). Furthermore, the reverse transmission of sound from the cochlea to the ear also reduces rapidly with high frequencies which affect OAEs but not the HTL (Puria, 2003). A third source of inter-subject variability in DPOAEs both at CAF and EHF ranges is the presence two separate DP-generation mechanisms – the so-called "distortion source" and "reflection source" components. These can interfere with each other, weakening the correlation between the measured DPOAE and HTLs. Similarly, TEOAE amplitudes are affected not only by OHC function, but also by the potency of reflection sites along the BM, thought to arise from impedance inhomogeneities. This is an additional source of inter-subject variability in TEOAE that is unrelated to HTL variability both at CAF and EHF ranges.

Furthermore, inconsistencies in the findings with previous studies that reported changes in EHF-DPOAEs before the CAF range with noise exposure (Narniah et al. 2017; Dhrruvakumar et al., 2021), might be related to the reason that most participants in the current study were not frequently exposed to noise, making there NESI score lower than the studies included previously. Although the original planned analysis did not show an effect of NESI score on TEOAE and DPOAEs that reached statistical significance, an exploratory study did suggest that there may be an effect only on the participants with NESI scores in upper quartile. The effect may have been diluted in the planned analysis due to the high number of participants with low NESI scores. This suggests that the results in the study are not inconsistent with the hypothesis that EHF measures are strongly affected by noise exposure and may add predictive in assessing NIHL.

In addition, no changes in EHF-hearing measurement with the incremental increase in NESI score were seen with longitudinal data. This longitudinal part of the project was weakened by a high participant dropout rate.

From the current study findings, it was indicated that noise exposure was associated with EHF-HTL, which was previously reported by other studies in the literature. Thus, this measurement has the implication of detecting noise exposure earlier than CAF-HTL.

7.2.2 Measurements of EHF-OAEs in young adults

As there is paucity in the literature on the measurement of the EHF-OAEs, this project aimed to determine better ways to evoke EHF-OAEs and to assess which OAE stimulus paradigms were most strongly correlated with EHF HTLs, in a sample of young adults with various degrees of noise exposure (i.e. throughout chapters 3, 4, 5, and 6). It is well established that there are significant negative correlations between OAEs and HTL at CAF range (Sistoa et al., 2007; Guida et al., 2012). The current study found a similar negative correlation between HTL and both DPOAEs and TEOAEs at the EHF-range. It is likely that this might be similar to what has been already suggested in the CAF range, in which both HTL and OAE measurements share similar generation sources. In this suggestion, both HTL and OAE measurements are affected by the active amplification of the OHCs, with the greater amplification leading to lower HTL and higher OAE amplitude. In fact, at EHFs, it has been found that (65/55) are a better predictor of HTLs than (70/70), despite the lower SNRs. There isn't an obvious explanation for this. It may be because the OHC response is non-linearly related to stimulus intensity in a complicated way, perhaps due to intrinsic electromechanical non-linearity or due to efferent neural effects. This may lead to DPs at higher stimulus levels (i.e. 70/70) being less sensitive to OHC dysfunction than those at lower stimulus levels. Thus, it might indicate that this method might be effective is assessing the cochlear function at a single point in time, to provide information about the EHF-HTL for example in difficult-to-assess subjects. On the other hand, EHF-DPOAE (70/70) evoked greater amplitude and SNR than the lower stimulus level, which might indicate that this method might be useful to assess the progression of hearing over time in subjects exposed to noise such as health surveillance.

TEOAEs and DPOAEs at the EHFs showed a positive correlation; this is as expected because both share some mechanisms relating to their generation and transmission (such as active amplification and ME attenuation).

When comparing the EHF-TEOAE signals and SNR, collected with DE and RDNL EHF TEOAEs. There were similarities between the waveform of both paradigms, which suggests that the signals evoked from that region are genuine. In the current study, TEOAE SNR obtained using the DE paradigm had greater statistical significance than that obtained using the RDNL paradigm for stimulus levels of 65 and 75 dB peSPL using the HPF-stimulus.

In the current study, the SNR for EHF-TEOAEs was typically lower than for EHF-DPOAEs. For EHFDPOAEs, SNR for most of the subjects was > 3 dB, while for the EHF-TEOAEs, the SNR in many cases was < 3 dB. However, in study 3 when investigating which parameter might evoked greater SNR, finding indicated that the use of DE technique in the 9.4

½-octave band achieved an SNR that would be clinically useful (> 6 dB SNR). This finding may be the result either of the ME transfer function, which is less effective for higher frequencies (Puria, 2003), or from cochlear effects. Another explanation might be due to the EAC characteristics, where the calibration method is affected by a half-wave resonance which will tend to emphasise components around 8 kHz (Charaziak and Shera, 2017).

7.2.3 Cochlear physiology for HTL and OAE at EHF and the relationship with audiometric fine structure

Since there are a lot of things that are not fully understood in the EHF-hearing function, the study aimed to better understand what determines EHF HTLs and OAEs, and how they differ from HTLs and OAEs at CAFs. By assessing the cochlear mechanical behaviour in EHF and whether it is similar to what was seen in CAF range, in term of correlation between AFS ripple depth and both HTL-PTA and TEOAS at EHFs. From the current findings, no correlation was indicated between EHF-AFS and both TEOAEs and HTL at the EHFs. There might be a difference between the EHF-AFS and CAF-AFs, in that, the ripple depth at EHF-AFS is smaller in amplitude and less regular in its spectral periodicity than is seen at CAF range. Several possible causes for this difference: first, less OHC activity; second, less potent reflection sites near the characteristic place; third, the shape (width) of the TW envelope leads to less coherent reflection at the characteristic place (since the strength of the reflection depends on the width of TW envelope (Zweig and Shera, 1995) and finally, less basal reflection of the TW at the stapes.

7.3 Limitations of the Research

Listed below are the following limitations of the studies described in this research project:

- Although the aim of this study was to recruit subjects assumed to be highly exposed to noise, such as those from the music and audio technology departments, this was not as easy task to realise for several reasons. Firstly, due to the nature of the study, most of the subjects found it difficult to participate as this kind of study requires more than one visit over a certain period. Secondly, due to the time restrictions I have as a PhD student, starting data collection within a fixed planned schedule is preferable. Thirdly, it was necessary to start at a specific time to allow enough time for follow-up visits to be possible, but the study was limited here in not recruiting a sufficient number of subjects who are exposed to high-noise activities.
- Lifetime noise exposure was quantified with a NESI score, but as a self-reported measurement there might be some degree of error involved here. There was hence a serious possibility of underestimating or overestimating the subject exposure level, with

self-reporting likely to be a source of considerable random error and potentially bias error (even though NESI has been validated to a certain extent [Ferguson et al., 2019]).

- This study has also been limited by time restrictions as it was designed to monitor hearing changes over a two-year period. However, problems with equipment, recruitment, drop-outs and Covid-19 regulations led to these plans being revised. Owing mainly to the lockdown, the data collection for phase 2 had to be finished with any future scheduled testing cancelled, which left a total sample size of 26 for that phase.
- The main limitation in study 2 was related to the EHF TEOAE average frequency selection, where most of the energy was predominantly in the ½ octave band with a centre frequency of 6.7 and 9.4 kHz. This band has dramatically less energy with its centre frequency of 13.3 kHz (Figure 5.3 B), entailing that the OAE signals are biased towards the lower band octave, being that most of the information comes from that band (i.e. centred 6.7 and 9.4 kHz).
- Study 3 was then limited by the RDNL paradigm. There is a clear ringing in the waveform that might restricted the possible MLS click rates with the ER-2 earphones and with the HPF stimulus waveform. This phenomenon is likely due to the overlap of successive MLS stimuli within the OAE probe transducers leading to effects of transducer non-linearity. Such a problem could at least be partly overcome by using inverse filtering in the study, but this process presents the difficulty of only working if the exact acoustic of the cavity is known. In addition, what works for default clicks might not work for HPF here, as the latter requires filtering to boost the high frequency and the interaction between signals cannot be stopped.
- Although calibration was used with the standard ear simulator method, there is always the possibility of inter-subject variability due to EAC acoustics. Other calibration methods, such as the FPL method, might eliminate the issue of inter-subject variability but these approaches will still be time-consuming.
- The calibration for the OAE probe microphones, audiometer and OAE earphones and the ear simulators could have been more carefully managed, perhaps by controlling the temperature of the test booth. A more comprehensive calibration would have been beneficial immediately before and after every test session, particularly for the longitudinal study (Study 1B).

7.4 Future Possibilities for Research

Recommendations for future study projects are given in further list form here:

- A further longitudinal study is required to assess noise exposure effects on EHF-HTL and EHF-OAEs, with this research covering more than a 2-year period. More advanced calibration methods should be considered to calibrate the stimulus levels using the FPL method, and the OAE levels using the EPL methods. Such an approach would reduce the impact of inter-subject differences in EAC acoustics on the measurements.
- Assessment of the reliability of NESI score could compare the estimated noise exposure self-report with the dosimeter.
- As the EHF-HTL lacks standards that estimate NIPTS over the years as the one set for ISO 1999, further research is required to fill this gap.
- Assessment of other factors that might impact EHF hearing, such as ototoxic drugs, could be investigated with EHF- TEOAEs and DPOAEs to determining the earliest indicators of hearing changes.
- Further research should explore the frequency region between 4 and 10 kHz (for both CAF and EHF), being that this has not been examined by previous studies but this is where TEOAEs are more readily measured in the EHF region, as was seen in chapter 5.
- New studies are required to determine which stimulus levels are more applicable in evoking a greater signal from EHF-DPOAEs e.g., by measuring DPOAEs at various stimulus levels. Research could also determine which stimulus level was used to evoke DPOAEs better correlated with EHF-HTL i.e., correlated with EHF-HTLs in both cross-sectional and longitudinal studies.
- Currently, there are very few studies of the audiogram fine-structure in the 6-16 kHz regions, but further studies (similar to those in Chapter 5) of the relationship between AFS, TEOAEs and SOAEs in this frequency region would enable examination of the differences between cochlear function in the EHF- and CAF- frequency regions. These differences could include the frequency region down to 6 kHz, a calibration of TEOAEs using the EPL method and a larger sample allowing correlations in the population to be more accurately determined.
- Further research and development could be undertaken on the RDNL method to establish whether changes in the stimulus shape might reduce the detrimental effects of transducer non-linearity. Such a study may be best realised by using inverse filtering to reduce the temporal overlap of successive MLS stimuli.

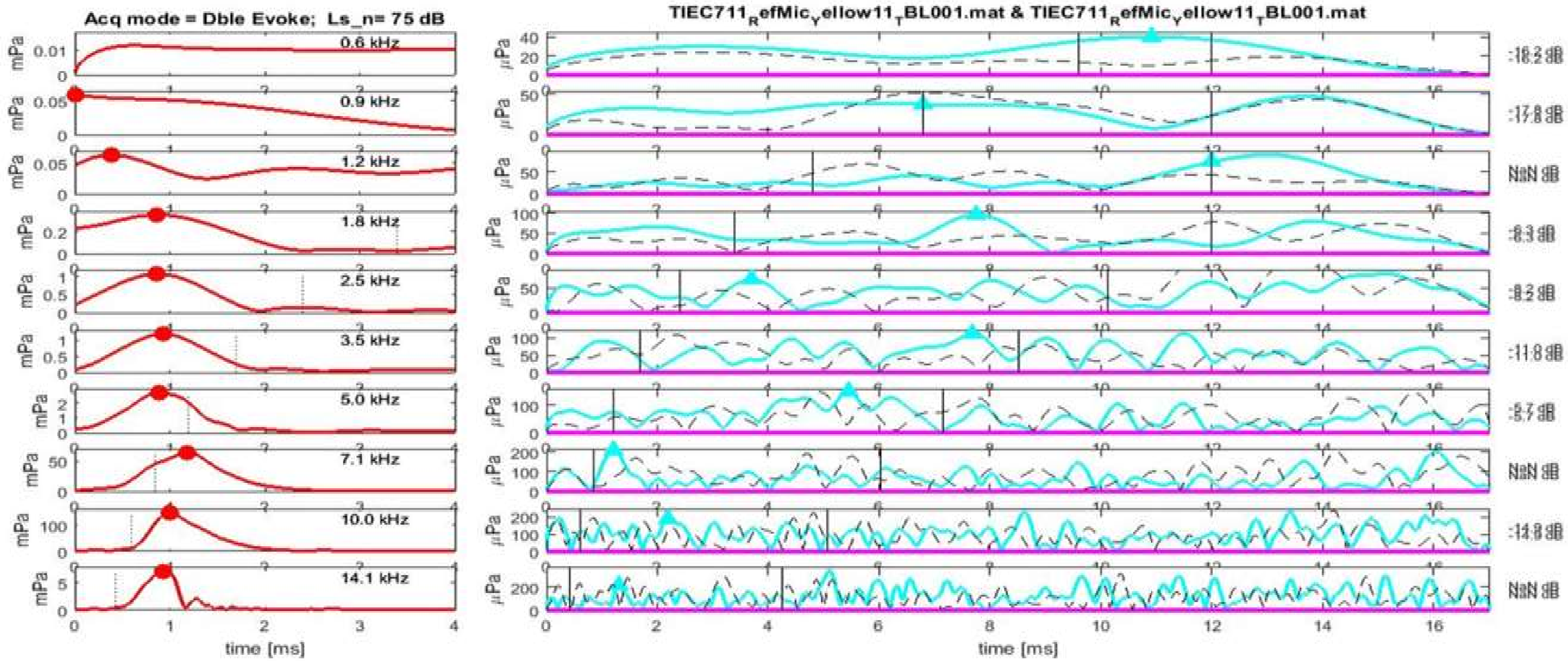
7.5 The Clinical Implications of this Research

Despite the limitations described, this study has provided a novel contribution to knowledge with regard to the use of EHF-TEOAEs and EHF-DPOAEs. These findings may have a direct relevance for clinical applications which are outlined below:

- This study detected that the EHF-DPOAEs (70/70) stimulus paradigm might be able to evoke a greater DPOAE signal amplitude and SNR at the EHF than the (65/55) paradigm. Therefore, a recommend of a higher stimulus level to provide a greater recording of DPOAEs with a clinically useful SNR (> 6 dB). This approach could then be used for clinical purposes in detecting any deterioration of OAEs and for monitoring hearing over time, especially in subjects with ototoxic drug use. Though the usefulness of this was not tested directly in the current project.
- A second implication of the current study derives from the assessment of EHF-TEOAEs with RDNL and DE. The findings here reported that using the HPF stimulus with DE technique in the 9.4-kHz ½-octave band was the only measurement that achieved a clinically useful SNR (> 6 dB SNR). A possible application is that the use of EHF-TEOAEs HPF with DE might have potential clinical use for assessing the TEOAEs at EHF.
- The (65/55) paradigm evoked EHF-DPOAEs with amplitudes demonstrating significantly higher correlation with EHF-HTLs than those evoked by the (70/70) paradigm.
- The correlation coefficient between EHF-HTLs and EHF-TEOAE amplitudes were not significantly different from the correlation coefficient between EHF-HTLs and EHF-DPOAE amplitudes. This finding suggests that EHF TEOAEs might be just as good at predicting EHF-HTLs as EHF-DPOAEs
- This study might confirm what has been suggested by previous studies that EHF-HTL might detect early signs of hearing changes due to noise. Consequently, this use of EHF-HTL for detecting changes and hearing monitoring may be useful for early intervention, such as in the use of hearing protection and changes in working practices for those who might have tender ears and work in noisy industries.

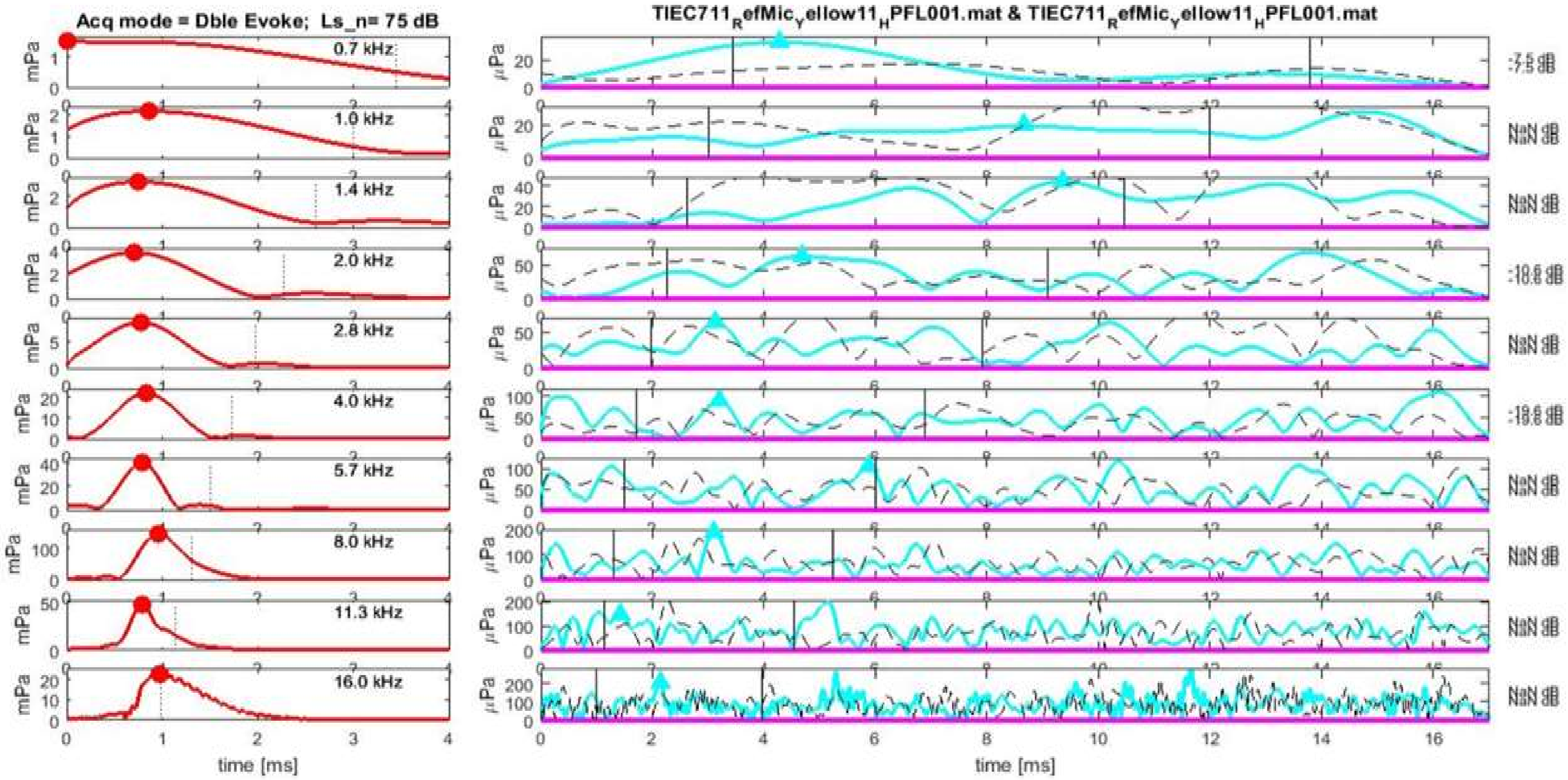
Appendix A DE measurements in ear simulator

Demonstrate that the DE paradigm is successfully eliminating the stimulus artefact, at least when making recordings in the ear simulator where you expect only noise to result.



Appendix A

Figure, TB measurements in ear simulator. The left-hand traces show the envelope of the stimulus after filtering using an 1/2-octave filter with the centre freq shown in each the left-hand panel, and before the stimulus artefact has been removed using the DE paradigm using TB. The red filled circle indicates the peak in the fitlered stimulus envelope. The right-hand traces show the resulting OAE trace, filtered using the same 1/2-octave filter as in the left hand panel, and after the stimulus artefact has been removed by the DE paradigm. The traces appear to show only residual noise, with no signs of a stimulus artefact in the right hand panel arising from measurements in the ear simulator. The two black vertical lines in each right-hand trace indicate the time window where OAEs are expected to appear, and over which the OAE signal and SNR are to be estimated. The estimated SNR is shown on the right of each right-hand trace. "NaN" indicates that the unbiased estimate of the signal RMS amplitude was negative, indicating that no signal could be detected at all. The negative estimated SNRs in all bands indicates that no significant stimulus artefact was detected in the ear simulator



Figure, HPF measurements in ear simulator. The left-hand traces show the envelope of the stimulus after filtering using an 1/2-octave filter with the centre freq shown in each the left-hand panel, and before the stimulus artefact has been removed using the DE paradigm using HPF. The red filled circle indicates the peak in the fitlered stimulus envelope. The right-hand traces show the resulting OAE trace, filtered using the same 1/2-octave filter as in the left hand panel, and after the stimulus artefact has been removed by the DE paradigm. The traces appear to show only residual noise, with no signs of a stimulus artefact in the right hand panel arising from measurements in the ear simulator. The two black vertical lines in each right-hand trace indicate the time window where OAEs are expected to appear, and over which the OAE signal and SNR are to be estimated. The estimated SNR is shown on the right of each right-hand trace. "NaN" indicates that the unbiased estimate of the signal RMS amplitude was negative, indicating that no signal could be detected at all. The negative estimated SNRs in all bands indicates that no significant stimulus artefact was detected in the ear simulator

Appendix B Noise exposure structured interview “noisy activities examples”

NESI THE NOISE EXPOSURE STRUCTURED INTERVIEW

Recreational Noise Examples

- Your interviewer has asked you to note any noisy activities you have experienced. Listed below are some common noisy activities, which may help to prompt your memory.
- **Remember what is meant by “noisy”:** situations causing you to **raise your voice** to communicate at a distance of 4 feet.
- **Do not restrict yourself to the activities on this list.** Also note any other noisy activities you have experienced.
- **Only note activities that you have found to be noisy.** If you have experienced an activity on this list but did not find it noisy, then **ignore it.**

Live music

Examples:
- Concerts
- Festivals

Nightlife

Examples:
- Nightclubs
- Bars
- Pubs

Making music

Examples:
- Playing/singing in a group
- Playing/DJing/singing solo

Listening though earphones and headphones

DIY noise

Examples:
- Power tools
- Powered gardening tools

Engine noise

Examples:
- Motorbikes
- Motorsports
- Motorboats

Sport-related noise

Examples:
- Sports matches
- Sailing

Cinema

Appendix

Noise exposure structured interview “Speech Communication table”

NESI THE NOISE EXPOSURE STRUCTURED INTERVIEW

Speech Communication Table

Vocal effort required	*Estimated level*
Talk normally from 4 feet	<80 dBA
Raise voice from 4 feet	87 dBA
Talk loudly from 4 feet	90 dBA
Talk very loudly from 4 feet	93 dBA
Shout from 4 feet	99 dBA
Shout from 2 feet	105 dBA
Shout in listener's ear	110 dBA

A guide for estimating unknown noise levels (of a continuous type) based on speech communication difficulty.

Approximate communication-limiting noise levels are based on the scenario of one person communicating with another in an environment that they are both used to, assuming that the listener is not hearing impaired, is not wearing hearing protection, and may be assisted to some extent by gestures and facial cues.

Noise exposure structured interview “head phones estimated level”.

Volume control setting	Estimated level
<70% of maximum	<80 dBA
70% of maximum	82 dBA
80% of maximum	88 dBA
90% of maximum	94 dBA
Maximum volume	100 dBA

Appendix C (NIPTS compared to the NESI score)

The NESI score is directly related to the SPL and exposure duration, as it quantifies the level and duration of exposure to each activity. It is proportional to the acoustic energy or "immitance" received by the person. For example, when applying the exchange rate of 3 dB A ;1 unit NESI score corresponds to 10 years of exposure at 80. See table 1

Table 1 unit of NESI score in relation to level and years of exposure.

NESI score units	Years of exposure	level of exposure dBA
1	10	80
2	20	80
2	10	83
2	5	86

One year equivalent to 8 hours per day, 5 days per week, 52 weeks in the year (LAqe).

The NESI score is a combination of Estimated level (dBA), and an exposure duration for each activity that is immitance.

The ISO 1999 document provides a formula for estimating the likely NIPTS for a given exposure level in dBA and exposure duration in years, but there are some complications:

1) The NIPTS estimation is affected by the large inter-subject variability, that results of the vulnerability to NIHL, so the population of sample in ISO are divided in to 10%, 50% (median) and 90% and the prediction of NIPTS depend on the distribution of the samples. For example, exposure for 10 years of 85 dBA at 4 kHz, the median is 5 dB, while the 10% and 90%-percentiles are 3 and 7 dB respectively for females (see ISO 1999 Table D.1 p20).
2) The NIPTS calculation depends on exposure level and duration, while the NESI score is a combination of both of SPL and duration (i.e both combined in single value).
   for instance the NIPTS will be different for 20 years of exposure at 80 dBA than for 10 years of exposure at 83 dBA, which have the same NESI score.
3) NIPTS estimated are for CAF up to 6 kHz.
4) NIPTS are different for Females than in males for a given exposure, but the difference are not considered to be great.

According to what mentioned above estimating the NIPTS from NESI, is possible when there is a certain assumption of exposure duration (i.e 5 or 10 years) along with the assumption that the noise level was at a roughly constant level. How a given NESI score might translate into an expected NIPTS is roughly estimated. For example, 10 units of NESI score would arise for 10 years of exposure to 90 dBA. ISO 1999 then predicts median NIPTS of 0, 2, 8, 11, and 7 dB at 1, 2, 3, 4, and 6 kHz respectively. So a 4-freq average of the median NIPTS (2, 3, 4, and 6 kHz) would be 7 dB for a NESI score of 10 (for females). This would be the NIPTS relative to an otologically normal ear. 8 kHz is not estimated in ISO, it was assumed to be 0 at 8 kHz, then the 5-freq average would be 28 /5=5.6 dB rather than the 7 dB for the 4-freq average.

Appendix D The statistical significance of adding the interaction term (noise exposure and frequency range)

The table below shows the statistical significance of adding the interaction term β_3 to the model. This was assessed using the change in "-2log(likelihood)" for the model with and without β_3, which can be tested using a chi-square distribution. The differences between the two models in "-2log likelihood" following the chi-square distribution with one degree of freedom is 3.84.

Table: The results of -2log likelihood difference and their significance when compared to one degree of freedom

EHF-Measurements	With interaction model	Without interaction model	Difference between the two models
HTL baseline vs Phase 1	-389.301	-390.618	1.31
HTL baseline vs Phase 2	-241.065	-247.344	6.279*
DPOAEs Amplitude Baseline vs Phase 1	- 425.794	-425.613	-0.181
DPOAEs Amplitude Baseline vs Phase 2	- 241.447	-240.756	-0.684
DPOAEs SNR Baseline vs Phase 1	-509.104	- 511.753	2.64
DPOAEs SNR Baseline vs hase 2	- 288.128	- 289.317	1.189
TEOAEs Amplitude Baseline vs Phase 1	- 420.345	-421.096	0.75
TEOAEs Amplitude Baseline vs Phase 2	- 257.910	-257.922	0.012
TEOAEs SNR Baseline vs Phase 1	- 453.679	- 454.401	0.722
TEOAEs SNR Baseline vs Phase 2	- 284.577	- 286.351	1.774

Appendix E **(Averaging the outcome into single value)**

Why was a step size of 5 dB used, instead of 2 or 1 dB?

The question is whether it is possible to use 5 dB steps to detect small changes in HTL, and why 2 dB steps were not used instead.

There are two reasons why the current study used a 5 dB step size for HTL detection.

1. Decreasing the steps size to 2 dB would increase the time required for threshold detection.
2. When the HTL is averaged across frequencies, using 5 dB step size does not limit the smallest detectable difference between the 6-frequency band average HTL (i.e. EHF-HTL). This is due to averaging across frequencies and rounding to the nearest value (i.e. 5 dB or 0 dB). For example, if HTL were detected for 2 individuals, as in the following table:

Subject #	8 kHz	10 kHz	11.2 kHz	12.5 kHz	14 kHz	16 kHz
1	1	2	4	0	3	4
2	2	3	5	1	4	3

The HTL of each frequency would be rounded to the nearest value.

Therefore, for Subject 1, these values would be 0, 0, 5, 0, 5, , and for Subject 2, they would be 0, 5, 5, 0, 5, 5.

These, added up and averaged, would mean that Subject 1 scored 2.5 and Subject 2 scored 3.3 dB HL.

So in this case, we can see that the technique managed on average to pick up 0.83 dB difference between subjects.

Appendix F **(Permission of using figure)**

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- FIG. 1. The electrical voltage pattern for four stimulus paradigms for recording TEOAEs.
- FIG. 3. Comparison of the normalized SNR computed for the three derived nonlinear (DNL)paradigms from Eqs

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