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Utility and effectiveness of Auditory Measures for detecting 'Hidden Hearing Loss' and/or Cochlear Synaptopathy

By

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PLAGIARISM DECLARATION

I (Andrea Pienaar), hereby declare that this dissertation is my own work. Where secondary material is used, it has been carefully acknowledged and referenced in accordance with the University of Pretoria Department of Speech-Language Pathology and Audiology's requirements.

I understand what plagiarism is and am aware of the University of Pretoria's policy regarding this matter.

19/11/2019

Andrea Pienaar

Date of declaration

Student number: 15204652

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- To Marius Gouws, thank you for being my daily encourager.

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LIST OF ABBREVIATIONS

ABR	Auditory Brainstem Response
AEP	Auditory Evoked Potential
AP	Action Potential
CS	Cochlear Synaptopathy
dB nHL	Decibels Normalised Hearing Level
DP	Distortion Product
ECochG	Electrocochleography
HHL	Hidden Hearing Loss
Hz	Hertz
kHz	Kilohertz
kΩ	KiloOhms
MEMR	Middle ear muscle reflex
OAE	Otoacoustic Emission
SGN	Spiral Ganglion Neuron
SP	Summating Potential
SPL	Sound Pressure Level
SSSR	Subcortical Steady State Response

FORMATTING

APA 6th edition manuscript format and referencing style was utilised in this dissertation

ABSTRACT

This study examined the effectiveness of auditory measures that past studies have proven to have potential use in a clinical test battery for identifying a hidden hearing loss and/or cochlear synaptopathy.

The auditory and neural functioning was compared between 20 participants with no reported history of noise exposure and 20 participants with a history of occupational noise exposure. Each group aged 18 - 35 years (M = 27.1 years, SD = 4.56 years), presented with clinical normal hearing. A between-group comparison, cross-sectional analytic study design was implemented. Audiologic measures included pure tone audiometry in the extended high frequencies, distortion product otoacoustic emissions (DPOAEs), middle ear muscle reflexes (MEMR), auditory brainstem response (ABR), electrocochleography (ECochG) and a digits-in-noise test.

The noise-exposed group presented with the following results that significantly differed from the non-noise-exposed group: elevated contralateral MEMR for 500 Hz and a 1000 Hz, a decrease in ABR wave V amplitude (rarefaction, condensation and alternating polarity), a decrease in ABR wave III amplitude (rarefaction and alternating polarity only), a shift in ABR wave V latency (condensation polarity only) and lastly a shift in the ECochG AP latency. No significant difference in test results were observed between the non-noise-exposed group and the noise-exposed group for the DPOAE-, extended high frequency audiometry- or digits-in-noise test.

Results suggested that the inclusion of contralateral MEMR's, the ABR as well as the ECochG test may be valuable tools in a test battery investigating hidden hearing loss and/or cochlear synaptopathy in populations presenting a noise exposure history similar to the nature of occupational noise. It was further postulated that the nature of the noise individuals are exposed to may play a role in the neural site of lesion and therefore in the effectiveness of the selected audiometric measure in identification of hidden hearing loss.

1. INTRODUCTION

The death of cochlear hair cells as well as spiral ganglion neurons (SGN) was historically assumed to be the primary cause of hearing loss resulting in varying degrees of difficulty in listening in noise. New research findings suggest that loss of inner hair cell synapses may be a key contributor (Kobel, Le Prell, Liu, Hawks, & Bao, 2017).

Synapses between the inner hair cells and the cochlear nerve terminals have recently been believed to be the most vulnerable parts of the inner ear (Liberman, Epstein, Cleveland, Wang, & Maison, 2016). Age-related and noise-induced hearing losses in humans are influenced by several factors (Kujuwa & Liberman, 2006). The contributions of, and interaction amongst these factors, can shape the nature and degree of a hearing loss. A study conducted by Gates, Schmid, Kujawa, Nam and D'Agostino (2000) suggests that an age-noise interaction occurs, which aggravates age-related hearing loss in ears that were previously damaged by excessive noise exposure (Gates et al., 2000).

Prolonged noise exposure can result in a temporary threshold shift (audiologic thresholds may fully recover) or a permanent threshold shift (thresholds stabilize at an elevated value) (Kujawa & Liberman, 2009). According to Kujawa and Liberman (2009) the assumption of damage reversal of the inner ear and no deferred consequences for auditory function after noise exposure, is inaccurate. This study suggests that damage due to noise can cause immediate, widespread and permanent hair cell synapse and cochlear neuron loss despite normal pure tone audiometric thresholds.

This permanent synapse loss between the inner hair cells and cochlear nerve fibres is known as cochlear synaptopathy (CS) (Furman, Kujawa, & Liberman, 2013). Numerous research studies have confirmed that cochlear synapses are highly sensitive to noise exposure and aging (Kujawa & Liberman, 2009; Sergeyenko, Lall, Liberman, & Kujawa, 2013), and that even a dramatic loss of synapses can be hidden behind a normal audiogram (Plack, Barker, & Prendergast, 2014; Schaette &

McAlpine, 2011). This subtotal of noise- and age-induced synapse loss does not cause elevation of behavioural or electrophysiological thresholds until it is around 80-90% complete (Salvi et al., 2017). For this reason CS has also been termed hidden hearing loss (HHL).

The initial findings of CS were discovered in mice (Kujuwa & Liberman, 2006). In these rodents, up to half of their inner hair cell/SGN synapses were absent after being exposed to noise, despite their hearing thresholds fully recovering when measured by auditory brainstem response (ABR). There is limited evidence in humans of a neuropathy caused by noise exposure similar to what have been witnessed in rodent studies (Plack et al., 2014). There is however evidence that an individual with a noise exposure history may show deficits in complex discrimination tasks, despite presenting with near-normal threshold sensitivity (Plack et al., 2014). To date there is no reported single clinical measure that is a reliable indicator for the diagnosis of a HHL (Mehraei et al., 2016). Past studies have used a combination of both electrophysiological and behavioural approaches to detect HHL and/or CS in humans (Kobel et al., 2017).

Two electrophysiological approaches frequently used by researchers are ABR and subcortical steady state responses (SSSR) (Kobel et al., 2017). A clear relationship between increased noise exposure history and decreased ABR wave I amplitude was reported for a population of “normal” hearing listeners who self-reported their exposure to recreational noise over the period of one year (Stamper, Johnson, & City, 2016). After the data was re-analysed according to gender, the association between increased history of noise exposure and decreased ABR wave I amplitude were found in females only (Stamper et al., 2016). Bramhall, Konrad-martin, Mcmillan and Griest (2016) conducted a study to determine whether there is an association between increased lifetime noise exposure history in young people with normal behavioural pure tone thresholds and decreased ABR wave I amplitudes. The ABR wave-I amplitude results were compared between veterans with history of noise exposure and non-veterans with no history of noise exposure. Despite both groups having normal pure tone thresholds, the ABR wave I amplitudes were reduced at

suprathresholds in the veterans who reported high levels of military noise exposure and in non-veterans who reported history of firearm use (Bramhall et al., 2016). In a recent study with a larger sample size, no reliable relationship was found between ABR amplitude and noise exposure history, or ABR amplitude and speech-in-noise test results, with recreational noise exposure being similar to that described by (Kobel et al., 2017; Stamper et al., 2016). Prendergast et al. (2016) confirmed and extended these findings in 129 participants with normal behavioural pure tone thresholds. During this study no relationship between noise exposure history and ABR amplitude, temporal listening tasks or speech-in-noise tasks were detected (Kobel et al., 2017).

A study conducted by Mehraei et al. (2016) suggested that the effects of masking noise on ABR wave V latency may be utilized to diagnose CS. Findings from aforementioned studies suggest that CS can be identified by a reduced amplitude of ABR wave I. Unfortunately, obtaining reliable ABR wave I amplitudes in humans can be challenging, limiting its clinical use. Mehraei et al. (2016) demonstrated the effect of masking noise on the more robust wave V latency, proving that it mirrors the changes of the wave I amplitude (Mehraei et al., 2016).

Liberman et al. (2016) conducted a study on college students with clinically normal hearing, who were classified into low-risk and high-risk groups, based on their noise exposure history. Otoacoustic emission (OAE) testing and click-evoked electrocochleography (ECochGs) were performed to determine cochlear function. Hearing sensitivity was evaluated using behavioural pure tone audiometry and word recognition tests were conducted to assess speech perception in quiet, as well as noisy environments. Electrocochleography results in the high-risk group demonstrated significant differences in waveform peaks Summating Potential; (SP) vs. Action Potential; (AP). These SP/AP ratio results were consistent with that of a selective neural loss. Significant deficits in difficult word-recognition were established in the high-risk group. Their difficulty in these tasks was associated with elevation of pure tone thresholds at extended high frequencies (10-16 kHz) (Liberman et al., 2016).

Conducting multiple different electrophysiological methods to detect HHL and/or CS would reduce possible false positive or negative outcomes from one specific test (Kobel et al., 2017). Therefore, additional testing beyond the ABR would be helpful for detecting a HHL and/or CS. Auditory steady-state responses (ASSRs) have traditionally been used to confirm elevated behavioural thresholds. Recently ASSRs have been used as a more sensitive measure for detecting deficits at supra-threshold sound levels (Attias, Karawani, Shemesh, & Nageris, 2014). Correlations between ASSR modulation detection threshold and speech-in-noise test outcomes have been reported (Manju, Gopika, & Arivudai Nambi, 2014). The evoked potentials that originate from a subcortical level are referred to as SSSRs, which can be distinguished from the cortical responses by their relatively high frequency content (Bharadwaj, Verhulst, Shaheen, Liberman, & Shinn-Cunningham, 2014). Subcortical steady state responses, more recently referred to as frequency following responses, reflects phase locking to temporal fine structure for frequencies up to about 1 kHz and is sensitive to amplitude modulation. Temporal phase locking is particularly strong in low spontaneous rate SGN, thus, frequency following response is sensitive for CS (Bharadwaj et al., 2014). Paul, Waheed, Bruce and Roberts (2017) studied the behaviour amplitude modulation and subcortical envelope following responses in participants with normal behavioural pure tone thresholds, but a different self-reported noise exposure history. Those with a history of higher lifetime noise exposure had on average smaller envelope following responses, which suggest poorer subcortical amplitude modulation encoding (Paul et al., 2017). Frequency following responses may be influenced by differences in central auditory processing as well as interference from central auditory regions. This causes variability issues in frequency following response approaches, similar to the ABR (Kobel et al., 2017).

Based on the response properties of low spontaneous rate SGNs, behavioural tests of temporal processing abilities should be sensitive to a HHL (Kobel et al., 2017). It has been suggested that an decrease in ABR wave I amplitude is likely to co-occur with a decreased ability to understand speech, especially in the presence of noise, as well as reduced auditory temporal processing ability (Bharadwaj et al., 2014). Past studies show evidence of noise exposure effects on behavioural auditory tasks,

despite presenting with audiometric thresholds within normal range. Kujala et al. (2004) conducted a study to determine whether a noise exposure history has an effect on cortical sound processing and attention control. The participants in this study presented with normal hearing and had no history of neurological diseases. Behavioural responses to speech-sound discrimination tasks together with mismatch negativity of brainstem responses; indicated impairment in noise-exposed participants. Furthermore, noise-exposed participants were more easily distracted by irrelevant sounds. This was evident from increased interference in task performance and atypical brain responses (Kujala et al., 2004). In a study conducted by Hope, Luxon and Bamiou (2018) the auditory processing of air force pilots (history of noise-exposure) in comparison to air force administrators (no history of noise exposure) were assessed. The exposed group had poorer speech-in-noise perception which may be an indication of noise-related impairment of auditory processing in retrocochlear pathways (Hope et al., 2018).

Contradicting findings by Prendergast et al. (2017) provided no significant perceptual deficits in young participants presenting with normal behavioural pure tone thresholds and an increased noise exposure history. The goal of this study was to determine which behavioural tests may be affected by CS. A variety of behavioural tests were conducted such as frequency and intensity difference limens, amplitude modulation detection, interaural phase discrimination, the digit triplet speech test, the co-ordinate response speech measure, an auditory localization task, a musical consonance task and a subjective report of hearing ability. None of their findings were statistically significant, further proving that the effects of HHL and/or CS are difficult to detect in young listeners with normal audiograms (Prendergast et al., 2017) Based on a combination of both electro-physiological methods and behavioural testing, the evidence for an connotation between CS and suprathreshold hearing status continues to develop (Kobel et al., 2017).

Moore, Hunter, and Munro (2017) also stressed the importance of measuring extended high frequencies. They suggest that it may be the most important measure to identify a HHL and/or CS. The importance of extended high frequency

measurement for HHL and/or CS was also supported in a study conducted by Furman et al. (2013). They recorded responses from single auditory nerve fibres in guinea pigs exposed to noise (4 to 8 kHz octave band at 106 dB SPL for 2 hours). Two weeks after exposure hearing thresholds recovered to normal, while suprathreshold ABR amplitudes were reduced. They hypothesized that neural loss was selective for the subgroup of auditory nerve fibres with low spontaneous rates and high thresholds (Furman et al., 2013).

Guest, Munro and Plack (2019) have examined the middle ear muscle reflex (MEMR) to determine whether there is a correlation between MEMR results and a history of noise exposure or speech in noise performance. MEMR's have been utilized due to potentially being a more sensitive measure than electrophysiological measures previously used to detect a HHL and/or CS (Guest, Munro, & Plack, 2019). The majority of recent findings showed no relationship between MEMR results and speech in noise performance or MEMR and history of recreational noise exposure for listeners with normal audiograms (Guest et al., 2019; Prendergast et al., 2017). Bramhall et al. (2016) suggested that more extreme noise exposures may be more synaptopathic and may potentially affect MEMR results as observed in rodent studies (Valero, Hancock, & Liberman, 2017).

Lastly, an objective measure that has frequently been utilized for detecting HHL is DPOAEs. DPOAEs have been reported to be one of the earliest tests to indicate damage due to noise exposure, despite an individual presenting with a "normal" audiogram (Barbee et al., 2018). Studies that utilized DPOAEs in their test battery, overall showed a positive association between HHL with noise- and/or aging and DPOAE abnormalities. This study suggests that DPOAEs may be useful in detecting loss of cochlear synapses if measured within 24 hours after noise exposure.

The electrophysiological and immunohistological methods that have been successful in measuring HHL and/r CS in animals, has been found to be nearly impossible to conduct in human studies. Therefore, reliable and minimally invasive tools, that allow for reasonable inferences about the degree of synaptic damage when interpreted, should be used as part of a comprehensive test battery (Kobel et al., 2017). It is

evident that there have been many approaches and methods used to diagnose HHL and/or CS; however researchers are still not confident what measurement or combination of tests can be used to reliably diagnose this type of hearing loss.

Further studies will greatly benefit the practice of audiology as the diagnosis of HHL and/or CS may provide the earliest sign of both noise- and age- related hearing loss (Fernandez, Jeffers, Lall, Liberman, & Kujawa, 2015). This study aims to identify and confirm the most accurate combination of tests that may be utilized in order to diagnose HHL and/or CS. This will be conducted by exploring the effectiveness of utilizing audiological measures for detecting a HHL/CS.

2. METHODOLOGY

2.1. Research aim

This study aimed to examine the effectiveness of auditory measures that past studies has proven to have potential use in a clinical test battery for identifying a HHL and/or CS.

2.2. Research design

A between-group comparative, cross-sectional analytic research design was applied for this research study. A between-group comparative study design was implemented to determine and quantify the relationship between variables by observing two groups with different circumstances (noise-exposure background) (Bukhari, 2012). The auditory and neural functioning of individuals that present with a history of occupational noise exposure (noise-exposed group) versus individuals with no reported occupational or recreational noise overexposure history (non-noise-exposed group) were tested. Differences in these test results gave the researcher an indication of which audiologic test, or combination of tests were more sensitive to identifying a HHL or CS. Data obtained from this study was quantitative in nature. For the participants presenting without a history of occupational noise exposure the term “non-noise-exposed” group were used rather than the term “control” group. The term “control” group would’ve suggested that the group without occupational noise had no

noise-induced damage to their auditory system. The researcher only assumed no noise-induced damage in the non-noise-exposed group, but did not have objective measures to prove it, thus the term “control” group were avoided.

2.3. Ethical considerations

Informed consent

- This study was approved by University of Pretoria’s Faculty of Humanities’ Research Proposal and Ethics Committee, and was granted ethical clearance before any data collection took place (Appendix A).

- Permission to approach the industry to partake in the study and to conduct assessments on their site was obtained through a letter to the industry (Appendix B). In the letter, information regarding the study purpose, risks, benefits and confidentiality were provided to the chief executive officer.

- Written information about the study was provided to each participant who took part in this study. All participants were encouraged to ask questions if they were unsure about any aspects of the study.

- Thereafter, an informed consent letter was signed by all research participants; the noise-exposed group and the non-noise-exposed group (Appendix C and Appendix D). These letters contained a thorough explanation of all test procedures. The informed consent letters also reminded participants that participation in the research is voluntary, and that the researcher will stop the testing procedure at any point should they not want to continue.

Risks and safety

Participants who partook in this study were at minimal risk as these tests were not invasive. None of the tests performed during the study were harmful to the auditory system.

Anticipated benefits

Participants obtained a comprehensive hearing evaluation at no cost. If a participant was identified with a hearing loss or pathology that they were unaware of, he/she was referred to a health care professional that adhered to his/her needs.

Confidentiality

All participants were informed that data gathered would be kept confidential. Random subject numbers were allocated to each participant's data collection sheet, after which all personal identifiers were removed.

Data retention

The data will be stored at the Department of Speech-Language Pathology and Audiology at the University of Pretoria for a minimum of 15 years. It will be stored as hard copy and in electronic format.

Manuscript preparation

The final product is accurate and complete. It includes the following sections as per ASHA (2009) guidelines: title and abstract; review of literature; selection of methodologies; report of results and discussion.

2.4. Participants

Forty participants (20 noise-exposed and 20 non-noise-exposed) were recruited for testing. Participants were between the ages of 18-35 years (i.e., M = 27.1 years, SD = 4.56 years). The age restriction was applied to reduce the risk of discovering age dependent changes in hearing thresholds and cognitive function (Lineweaver, Salthouse, Fristoe and Coon, 1995). Males and females were tested (20 females) and a test ear was randomly chosen for each participant. The 20 participants in the non-noise-exposed group were obtained through non-probability purposive sampling (volunteers at the University of Pretoria Speech-Language Pathology and Audiology Department). The noise-exposed group were recruited from an industry where workers are exposed to occupational noise daily (non-probability purposive sampling). Although the noise-exposed group were exposed to occupational noise daily, all participants indicated that hearing protection were warn when they worked

in high noise level areas. The non-noise-exposed group had no reported history of occupational or recreational noise exposure, whilst the noise-exposed group had a minimum of two years history of occupational noise for ± 6 hours a day.

Each participant completed a noise exposure questionnaire (Appendix E) prior to testing. The questionnaire provided the researcher with information such as participant age, gender, total years exposed to occupational noise, type of hearing protection used and any ear-related problems if present. All participants were required adhere to an inclusion and exclusion criteria explained by table 1, table 2 and table 3.

Participants from the noise-exposed group were required to adhere to the following inclusion criteria:

Table 1: Inclusion criteria for noise-exposed group

Inclusion criteria	**Rationale**
History of noise exposure as indicated through a questionnaire (Appendix E)	Numerous research studies have confirmed that cochlear synapses are highly sensitive to noise exposure and aging (Kujawa & Liberman, 2009; Sergeyenko et al., 2013), and that even a dramatic loss of synapses can be hidden behind a normal audiogram (Plack et al., 2014; Schaette & McAlpine, 2011) This study compared the results of various audiological measures between a group of participants presenting with a history of occupational noise exposure (at high risk of presenting with a HHL and/or CS) and a group of participants with no history of noise-exposure (at low risk of presenting with a HHL and/or CS).
No history of otologic and/or neurologic disease	Otologic disease includes a range of infectious, metabolic, Immunologic, Idiopathic and bone diseases of the ear (Merchant & Nadol, 2010). Increasing evidence demonstrates how synapse functioning is a major determinant of several neurologic diseases (Lepeta et al., 2016). Thus test results may have been influenced by otologic or neurologic disease, rather than synapse loss due to noise exposure.
Normal audiometric thresholds (125-8000Hz)	This study suggested that damage due to noise could cause immediate, widespread and permanent loss of hair cell synapses and cochlear neurons despite normal pure tone audiometric thresholds (Kujawa & Liberman, 2009). Therefore, participants who potentially presented with a HHL and/or CS would

	have presented with normal audiometric thresholds.
Age 18-35 years	Presbycusis is known to emerge as one is aging, for this reason; an age limit was implemented for this study. As the age of the individuals increased, so did the risk of presenting with age related changes to the auditory system (Ferrite & Santana, 2005). According to Ferrite and Santana (2005) age related changes can affect both the inner and outer hair cells found in the cochlea, afferent neural fibres and the stria vascularis. A cut off age was specified so that the effect of noise exposure on HHL/CS could be identified independently from an age related hearing loss/pathology.
Proficient in English	Participants were required to understand English on a conversational level, as information and instructions during the study were given in English. The speech-in-noise test also required the participants to listen and respond to English stimuli.

Participants from the non-noise-exposed group were required to adhere to the following inclusion criteria:

Table 2: Inclusion criteria for non-noise-exposed group

Inclusion criteria	**Rationale**
No history of occupational or recreational noise indicated through a questionnaire (Appendix E)	The non-noise-exposed group were required to present with no occupational of recreational noise exposure history as they would've then (similar to the noise-exposed group) also been at risk for presenting with a HHL and/or CS.
No history of otologic or neurologic disease	Due to possible effects on test results (refer to Table 1)
Normal audiometric thresholds (125-8000Hz) in both ears	Due to the nature of a HHL and/or CS (normal audiometric thresholds) (Refer to Table 1)
Age 18-50 years	Due to age-related changes to auditory system. (Refer to Table 1)

Proficient in English	Due to language of instructions and speech-in-noise test (Refer to Table 1)

The exclusion criteria for both the noise-exposed and non-noise-exposed group were as follows:

Table 3: Participant exclusion criteria

Exclusion criteria	**Rationale**
Participants that presented with otologic or neurologic disease	Due to possible effects on test results (Refer to Table 1)
Participants <18 or >35 years old	Due to the effects of aging on the auditory system ((Refer to Table 1)
Participants that were not proficient in English	Information and instructions during this study were given in English. (Refer to Table 1)

2.5. Research setting

Data collection for the noise-exposed group took place in a quiet room at the industry. Records from the industry were accessed to evaluate previous hearing screening results. These records were not used as part of data collection, but rather to get an indication of which participants could potentially be approached for this study. Data collection for the non-noise-exposed group took place in a quiet room at the Department of Speech-Language Pathology and Audiology, University of Pretoria. Recruitment of individuals who took part in this study was based on the inclusion criteria (Table 1) and exclusion criteria (Table 2). All tests were performed on the same day at the same sitting for each participant.

2.6. Materials and apparatus for participant selection

Participants had to present with normal results for the following tests in order to undergo further data collection.

Table 4: Auditory tests for participant selection criteria

Test	Purpose	Instructions to the participant	Normal test results	Abnormal test results
Otoscopy Welch Allyn Pocketscope	Determined whether the individual presented with any outer-ear abnormalities. The tympanic membrane and ear canal was examined (Fincher, 1994).	To sit up straight, face forward and keep head still during examination.	Healthy looking ear canal with minimal wax and no redness/skin irritation observed. Healthy looking tympanic membrane with a light reflex present.	Conductive pathologies present such as excessive wax, red ear canal, bulging or perforated ear drum.
Tympanometry Interacoustics Titan – IMP440 (Impedance module). Tympanometry 226Hz – Automatic (flexible start and stop pressure).	Determined middle-ear functioning (pressure, compliance and volume) and the absence of otitis media (Lous, 2015).	To be seated in an up-right position facing forward. The participant was informed that a slight pressure would be felt, but that he/she was not required to respond to anything.	Type A tympanogram for adults defined as: • Middle Ear Pressure: -50 - +50 daPa • Compliance: 0,3-1,8 ml (Hunter & Shahnaz, 2016)	Middle ear pressure and compliance that fell outside these normal ranges of: • Middle Ear Pressure: 50 - +50 daPa • Compliance: 0,3-1,8 ml (Hunter & Shahnaz, 2016)
Pure tone Audiometry KuduWave 5000 by eMoyo (Pty) Ltd using insert foamtips.	Determined hearing sensitivity (125-8000 Hz). Pure tone audiometry involved the peripheral and central auditory system (Kutz &	To press a button when sound was heard. When bone conduction testing was needed, participants were asked to ignore the background noise	Pure tone air conduction and bone conduction thresholds ≤ 20 dB HL. (Brännström, Karlsson, Waechter, & Br, 2018).	Air conduction/ bone conduction thresholds ≥ 20 dB HL. (Brännström et al., 2018)

	Meyer, 2020).	and to only listen for the sound stimuli presented.		

2.7. Procedures for participant selection

The following procedures were conducted to determine participant selection/inclusion to partake in this study.

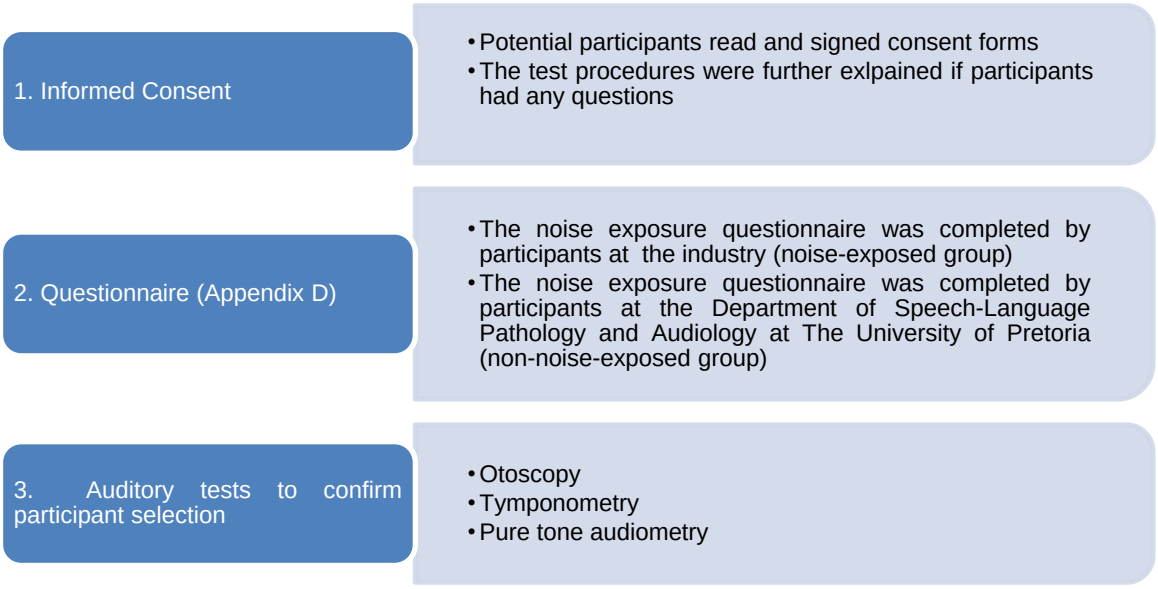

Figure 1: Participant selection procedure

- Potential participants were asked to read and sign participant information and consent letter (Appendix C/D). Thereafter, all participants filled in a health and noise exposure history questionnaire (Appendix E). The questionnaire was filled in alongside the researcher to ensure that the participant understood all questions asked and that all questions were filled in as comprehensively as possible. The questionnaire provided the researcher with information such as participant age, gender, years of being exposed to occupational noise, type of hearing protection used and any ear-related problems if present.
- Otoscopy was performed using a Welch Allyn pocket scope. The participant was asked to sit upright whilst the researcher examined his/her outer-ear.

- Tympanometry was performed to confirm normal middle-ear status. Participants sat upright and faced forward whilst a probe was placed in the ear-canal and measurements were taken.
- Pure tone audiometry took place in a quiet room. The participant was instructed to press a respond button when the sound was heard. Sounds were conducted through circumaural insert earphones. Air conduction testing was documented at 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. Bone conduction testing was administered via a bone conductor placed on the forehead, and documented at 250, 500, 1000, 2000 and 4000 Hz.
- Information from the health and noise exposure questionnaire (Appendix E), as well as the test results obtained from otoscopy, tympanometry and pure tone audiometry confirmed participant selection. The noise-exposed group as well as the non-noise-exposed group were required to present with normal auditory test results for above mentioned measures.

2.8. Materials and apparatus for data collection

Tests used for data collection were based on the equipment that had been utilized by past studies to identify HHL and/or CS.

Table 5: Tests and equipment for data collection

Test	**Purpose**	**Instruction to participant**	**Protocol/Parameters**
Extended high frequency audiometry The hearX (hearTest) application was used, installed on a Samsung Galaxy A3 smartphone. Sound was conducted through circumaural sound-attenuating Sennheiser HDA200 headphones.	Determined hearing sensitivity/thresholds at extended high frequencies (10 000, 12 500 and 16 000 Hz). Pure tone audiometry involved the peripheral and central auditory system (Kutz & Meyer, 2020).	To press a button on the screen of the smartphone when tone is heard.	Measured at 10 000, 12 500 and 16 000 Hz.

<table>
<tr>
<td>Diagnostic DPOAE (Distortion product otoacoustic emission) testing

Interacoustic Eclipse EP 25 auditory evoked (AEP) response system.</td>
<td>Determined cochlear function, more specifically the outer hair cell integrity (Abdala & Visser-Dumont, 2001).</td>
<td>To sit still and face forward whilst a probe will be inserted into the ear canal.</td>
<td>Using the DPOAE20, calibrated in accordance with ISO 389-9 (2014).

Detailed protocol conducted from 500Hz – 8000Hz, measuring 8 points per octave.

Intensity of 65 dB (L1) and 55 dB (L2).

F2/F1 ratio of 1, 2.</td>
</tr>
<tr>
<td>Middle ear muscle reflexes

Interacoustics Titan – IMP440 (Impedance module).</td>
<td>Determined the presence of a MEMR mediated by the inner hair cells, eighth nerve, and brainstem pathways (Berlin et al., 2005) .</td>
<td>To sit still and face forward while a probe is placed in the ear-canals for measurement.</td>
<td>MEMR with single intensities at 500, 1000 and 2000Hz –ipsilateral (automatic).

MEMR with single intensities at 500, 1000 and 2000Hz– contralateral (automatic).

Threshold was determined when a change in compliance of 0,02 ml was present at probe tone frequencies (Guest, Munro, Prendergast, & Plack, 2019).</td>
</tr>
<tr>
<td>Neurological ABR

Interacoustic Eclipse 25 auditory evoked (AEP) response system.</td>
<td>Determined the neural integrity of the auditory nerve up to brainstem level (Weber, 1979).</td>
<td>To lie comfortably on a bed and relax all muscles during the ABR examination.</td>
<td>Parameters:
<table>
<tr><td>Stimulus type</td><td>Click</td></tr>
<tr><td>Stimulus intensity</td><td>80 dB nHL</td></tr>
<tr><td>Stimulus rate</td><td>30Hz (17,1 stimuli per second)</td></tr>
<tr><td>Stimulus polarity</td><td>x1 rarefaction

x1 condensation</td></tr>
<tr><td>Number of sweeps</td><td>Minimum 4000</td></tr>
<tr><td>Filter Settings</td><td>30 – 3000Hz</td></tr>
<tr><td>Analysis time/ window</td><td>10 ms</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>ECochG

Interacoustic Eclipse EP 25 auditory evoked (AEP) response system.

TM electrode: consisted of thin wire protected by a plastic coating. The wire was hooked onto a cotton tip and insulated by pumbing tape.</td>
<td>Determined the auditory nerve response to stimuli, more specifically recorded the electrical potentials derived from the cochlear (Gibson, 2017).</td>
<td>To lie comfortably on a bed and relax all muscles during the ECochG examination.</td>
<td>Parameters:
<table>
<tr><td>Selected protocol</td><td>ECochG Click</td></tr>
<tr><td>Stimulus type</td><td>Click</td></tr>
<tr><td>Stimuli per sec.</td><td>11,3</td></tr>
<tr><td>Stimulus intensity</td><td>90 dBnHL</td></tr>
<tr><td>Stimulus polarity</td><td>Alternating</td></tr>
<tr><td>Number of sweeps</td><td>1500</td></tr>
<tr><td>Filter settings</td><td>High pass: 5000 Hz

Low pass: 3.3 Hz 6/oct</td></tr>
</table></td>
</tr>
<tr>
<td>Speech-in-noise test

Using the HearDigits (by hearX group) application installed on a Samsung Galaxy J2 smartphone.

Sound was conducted through circumaural sound-attenuating HD 280 PRO headphones.</td>
<td>Determined the effects of background noise on speech recognition abilities of participants (Le Prell & Clavier, 2017).</td>
<td>To carefully listen at the 3 numbers heard in presence of noise.

To enter the numbers heard on a keypad and press “OK” in order for the next 3 numbers to play.</td>
<td></td>
</tr>
</table>

2.9. Procedures for data collection

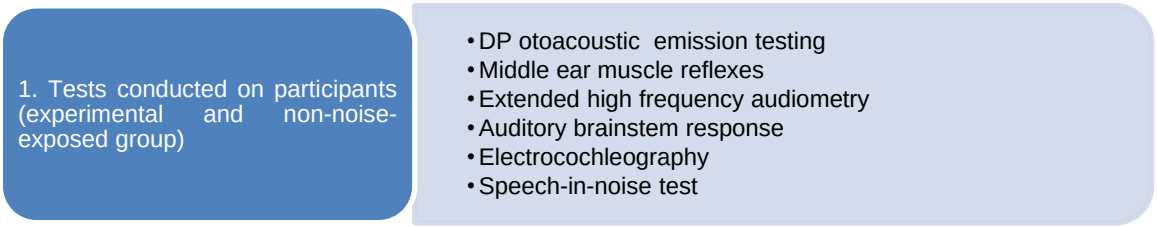

Figure 2: Data collection procedure

- DP otoacoustic measures were measured whilst participants were in an upright position facing forward. Participants were given instructions where after a probe was placed in the participant’s ear. A probe check was done prior to testing, if the probe check curve was steady and calm (this indicates

an airtight seal and low noise) the researcher commenced with testing. Sounds were presented to the participant and a response from the outer hair cells of the cochlea was measured. After the DP responses (8 points per octave) were measured, it was converted into half octave frequency bands to make it comparable to the audiometric frequencies obtained. This was done by using the following formula:

- **Step I:** conversion of dB SPL into the raw Pascal (pressure) units: Formula: *Raw Pascal value= (antilog (dB value/20)* 0,00002))*
- **Step II:** averaging the Pascal units by taking the mean value of different octave bands together (1, 2, 3, 4, 6 and 8 kHz).
- **Step III:** converting the mean half-octave band values back to dB SPL Formula: *dB SPL = 20 * Log10 (Pascal/0,00002)*

- Extended high frequency audiometry took place in a quiet room. Instructions were given to participant, where after the extended high frequency headphones were placed on the participant's head. Air conduction testing was documented at 10 000, 12 500 and 16 000 Hz. The results were available immediately after the testing was complete via a virtual audiogram displayed on the smartphone screen. This smartphone application has been validated for the testing of extended high frequencies (Bornman, Swanepoel, Biagio de Jager, & Eikelboom, 2019). Calibration was performed on the calibration feature of the hear Test application.

- MEMR measurements were obtained whilst the participant was sitting in an upright position facing forward. A probe was placed in the ear canal and no active participation was required from the participant.

- For the neurological ABR, two waves rarefaction and two waves condensation were measured with an artefact rejection level set at 40 µV. Participants were in a comfortable laying position with their eyes closed for the duration of the test. Reusable gold cup electrodes were prepared with Ten20 electrode paste. A two channel-electrode configuration was used. The skin was prepared with

Nuprep prepping gel before placing the inverting electrode on the ipsilateral mastoid, non-inverting electrode on the high forehead (Fz), and with ground at lower forehead (Fpz). The electrode impedance was monitored and accepted once impedance was <5 kΩ or below (Crumly, 2009). An ER-3A insert earphone with soft foam ear tips was used as transducer. Wave I, III and V latencies, amplitudes and interpeak latencies were recorded for rarefaction, condensation and alternating polarity.

- The participant was then asked to remain in his/her laying position for the electrocochleography measure. A tympanic membrane (TM) (inverting) electrode prepared with saline solution and conductive gel was inserted inside the ear canal and carefully placed onto the tympanic membrane. Reusable gold cup surface electrodes were prepared with Ten20 electrode paste. The skin was cleaned with Nuprep prepping gel before placement. The non-inverting electrode was placed on the on high forehead (Fz) with the ground electrode on low forehead (Fpz). A soft insert ear tip (ER-3A) was placed in the test-ear canal to conduct the stimuli and keep the TM electrode in position. Electrode impedance for surface electrodes was acceptable at <5 kΩ and for TM electrode at <20 kΩ (Crumly, 2009). The ECochG measurement was repeated in order to confirm repeatability of the wave.

  For ECochG ratio calculation the SP/AP area ratio was measured. This was done by first marking the start of the baseline (BLst). Baseline end (BLe) was marked by the software automatically (at the next point in the waveform where the amplitude crosses the baseline). Thereafter the SP, AP1, AP peak and AP2 was marked by the researcher (Ferraro, 2011). The area ratio was automatically calculated by the software.

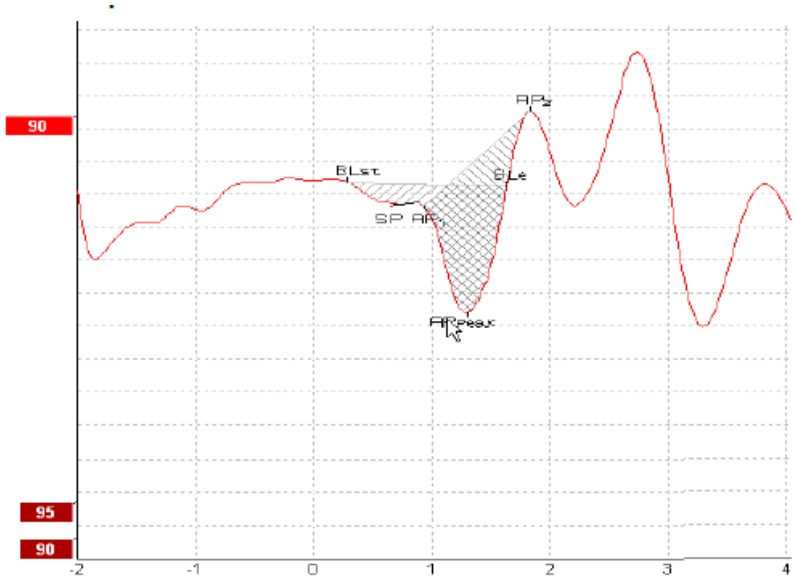

Figure 3: Example of marked points for area ratio

- The participant lastly completed a speech-in-noise test (hearDigits). The participant was given instructions and the headphones were placed on his/her head. The software installed was calibrated to ISO 13485 calibration standards. Participants responded to digit triplets in noise by typing in numbers on the screen that were heard. The digits were spoken by a female speaker with natural intonation, for example, 3–7–1, spoken as three–seven–one. The first set of digits was presented at the participant's comfortable listening intensity. After responding to 25 sets of digit-triplets, a signal-to-noise ratio was calculated by the application to give an indication of the participant's word recognition abilities in noise.

2.10. Data analysis

Data was recorded and analysed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25)**.** Wave analysis for ABR and ECochG had to be agreed on by two experienced audiologists. Mean, standard deviation (SD) and box plots were used to describe diagnostic test results. A one-way analysis of variance (ANOVA) was used for this study as the main interest of analysis focussed on the

difference in variables (history of noise exposure) on the two groups (Kim, 2017). Thus, any statistically significant differences between the means of the non-noise-exposed group and the noise-exposed group were determined. For comparison of absent MEMR's obtained from both groups, the chi-square test for homogeneity was used to determine whether differences in number of reflexes absent were consistent with being explained by different sampling alone (D. Johnson, H. Burton, A. Beyl, & E. Romer, 2015). An alpha value of $p < 0.05$ was used to indicate level of significance.

2.11. Reliability and validity

The goal of this study was to use measurements that is reliable and that yielded consistent results; reliability was ensured by the following:

- All tests conducted were administered in a consistent manner across all participants by a skilled student audiologist.
- Instructions for all tests conducted were similar for all participants.
- The modified Hughson-Westlake method (Carhart & Jerger, 1959), was utilized to determine behavioural pure tone thresholds.
- There was adequate construct validity throughout the study, as all equipment and measurements selected were appropriate to test the hypothesis.
- In this study, there was high face validity for the measurements, as all measuring instruments in the methodology were calibrated and validated for the use of their specific measure.

3. UTILITY AND EFFECTIVENESS OF AUDITORY MEASURES FOR DETECTING 'HIDDEN HEARING LOSS' AND/OR COCHLEAR SYNAPTOPATHY

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3.1 Abstract

Purpose: To examine the effectiveness of auditory measures that past studies have proven to have potential use in a clinical test battery for identifying a HHL and/or CS.

Method: The auditory and neural functioning was compared between 20 participants with no reported history of noise exposure and 20 participants with a history of occupational noise exposure. Each group aged 18 - 35 years (M = 27.1 years, SD = 4.56 years), presented with clinical normal hearing. A comparative within participant, cross-sectional analytic study design was implemented. Audiologic measures included pure tone audiometry in the extended high frequencies, middle ear muscle reflexes (MEMR), distortion product otoacoustic emissions (DPOAEs), auditory brainstem response (ABR), electrocochleography (ECochG) and a digits-in-noise test.

Results: The noise-exposed group presented with the following results that statistically differed from the non-noise-exposed group: elevated contralateral MEMR for 500 Hz and a 1000 Hz, a decrease in ABR wave V amplitude (rarefaction, condensation and alternating polarity), a decrease in ABR wave III amplitude (rarefaction and alternating polarity only), a slight shift in ABR wave V latency (condensation polarity only) and lastly a shift in the ECochG AP latency. No

significant difference in test results were observed between the non-noise-exposed group and the noise-exposed group for the DPOAE-, extended high frequency audiometry- or digits-in-noise test.

Conclusions: Results suggested that the inclusion of contralateral MEMR's, the ABR as well as the ECochG test may be valuable tools in a test battery investigating HHL and/or CS in populations presenting a noise exposure history similar to the nature of occupational noise. It was further postulated that the nature of the noise individuals are exposed to may play a role in the neural site of lesion and therefore in the effectiveness of the selected audiometric measure in identification of hidden hearing loss.

Key words: Hidden hearing loss, cochlear synaptopathy, noise-induced hearing loss, occupational noise

3.2. Introduction

Synapses between the inner hair cells and the cochlear nerve terminals have recently been believed to be the most vulnerable parts of the inner ear. In the aging and/or noise-exposed ear, these synapses degenerate prior to hair cell damage (Liberman et al., 2016). It is well known that prolonged noise exposure can result in a temporary threshold shift (behavioural thresholds recover fully) or a permanent threshold shift (thresholds stabilize at an elevated value) (Kujawa & Liberman, 2009). According to Kujawa and Liberman (2009) the assumption of damage reversal of the inner ear with no deferred consequences for auditory function after noise exposure, is inaccurate.

Kujawa and Liberman (2009) suggest that damage due to noise can cause immediate, widespread and permanent loss of hair cell synapses and cochlear neurons despite normal pure tone audiometric thresholds. Neural damage caused by noise and/or aging does not affect hearing thresholds until 80-90% of the neural synapses are damaged (Salvi et al., 2017). Various degrees of neural damage (<80%) may contribute to difficulty listening in noisy environments and may also have a key role in the generation of hyperacusis and tinnitus (Liberman et al., 2016).

Auditory disorders with similar aetiologies has been termed hidden hearing loss (HHL), due to the damage being “hidden” behind a “normal” audiogram (Barbee et al., 2018). Past studies have used the term HHL synonymously with the term cochlear synaptopathy (CS), however loss of ribbon synapses may not always be the cause of HHL (Barbee et al., 2018). Hidden hearing loss have thus also been termed auditory synaptopathy or cochlear neuropathy due to the site of lesion and the neurological effects of the specific loss (Zheng & Guan, 2018).

HHL and/or CS can be challenging in the practice of audiology. Patients may seek help with complaints of tinnitus, hyperacusis and inability to understand speech in noise, only to find out that formal testing does not validate what they are experiencing. Clinicians are left feeling helpless due to inability to diagnose or treat the patient’s symptoms (Barbee et al., 2018). There is little direct evidence of a noise-induced neuropathy in humans similar to that witnessed in rodent studies (Plack et al., 2014). There is, however, evidence that an individual with a history of excessive noise exposure may show deficits in complex discrimination tasks, despite presenting with near-normal threshold sensitivity (Plack et al., 2014).

Past studies have used a combination of both electrophysiological and behavioural approaches to detect HHL and/or CS in humans (Kobel et al., 2017). To date there is no reported single clinical measure that is a reliable indicator for the diagnosis of a HHL and/or CS (Mehraei et al., 2016).

Two electrophysiological approaches frequently used by researchers are auditory brainstem response (ABR) and electrocochleography (ECochG). A clear association between increased noise exposure history and decreased ABR wave-I amplitude was reported for a population of “normal” hearing listeners who self-reported their exposure to recreational noise over the period of one year. Bramhall, Konrad-martin, Mcmillan and Griest (2016) compared the ABR wave-I amplitude results between Veterans with a noise exposure history and non-Veterans with no history of noise exposure. Despite both groups having normal pure tone thresholds, suprathreshold ABR wave-I amplitudes were reduced in Veterans reporting high levels of military noise exposure (Bramhall et al., 2016). Contradicting findings by Liberman et al.,

2016 failed to detect a relationship between ABR amplitude and noise history, between temporal listening tasks and noise exposure, and between speech-in-noise tasks and noise exposure. These contradicting findings raise questions about duration of noise exposure as well as type of noise exposure that may contribute to a HHL and/or CS.

Liberman et al. (2016) classified college students with clinically normal hearing into low-risk and high-risk groups, based on their noise exposure history. ECochG results in the high-risk group demonstrated significant differences in summating potential; (SP) vs. action potential; (AP) waveform peaks. Significant deficits in difficult word-recognition were established in the high-risk group (Liberman et al., 2016). Based on the response properties of low spontaneous rate spiral ganglion neurons, behavioural tests of temporal processing abilities should be sensitive to a HHL (Kobel et al., 2017). In a study conducted by Hope, Luxon and Bamiou (2018) the auditory processing of a noise-exposed group had poorer speech-in-noise perception which may be an indication of noise-related impairment of auditory processing in retro cochlear pathways (Hope et al., 2018). Contradicting findings by Prendergast et al. (2017) provided no significant perceptual deficits in young listeners with normal audiometric hearing and an increased noise exposure history.

Moore, Hunter and Munro (2017) stressed the importance of measuring extended high frequencies in the noise-exposed population. They suggest that it may be the most important measure to identify CS. The importance of extended high frequency measurement for CS was also supported in a study conducted by Furman, Kujawa and Liberman (2013). They hypothesized that neural loss was selective for the subgroup of auditory nerve fibres with low spontaneous rates and high thresholds, thus measuring thresholds at extended frequencies may provide clinicians with early signs of a HHL (Furman et al., 2013).

Studies have examined the middle ear muscle reflex (MEMR) to determine whether there is a correlation between MEMR results and a history of noise exposure or speech in noise performance (Guest, Munro, & Plack, 2019). MEMR’s have been utilized due to potentially being a more sensitive measure than electrophysiological

measures previously used to detect a HHL and/or CS (Guest, Munro, & Plack, 2019). The majority of recent findings showed no relationship between MEMR results and speech in noise performance, or MEMR and history of recreational noise exposure for listeners with normal audiograms (Guest et al., 2019; Prendergast et al., 2017). Bramhall et al. (2016) suggested that more extreme noise exposures may be more synaptopathic and may potentially affect MEMR thresholds as observed in rodent studies (Valero, Hancock, & Liberman, 2017). Valero et al. (2017) found that the contralateral MEMR threshold was elevated and its maximum amplitude was attenuated in neuropathic mice.

Lastly, an objective measure that has frequently been utilized for detecting HHL and/or CS is DPOAEs. DPOAEs have been reported to be one of the earliest tests to indicate damage due to noise exposure, despite an individual presenting with a “normal” audiogram (Barbee et al., 2018). Studies that utilized DPOAEs in their test battery, overall showed a positive association between HHL with noise- and/or aging and DPOAE abnormalities. This study suggests that DPOAEs may be useful in detecting loss of cochlear synapses if measured within 24 hours after noise exposure. Failure to detect a relationship between HHL and altered DPOAE responses in past studies are better understood by considering the organization of the cochlear. The cochlear afferent innervation is of nature that 95% of cochlear afferent fibers are associated with inner rather than outer hair cells which are the generators for DPOAE responses (Spoendlin, 1972).

It is evident that there have been many approaches and methods used to diagnose HHL and/or CS. However researchers are still not confident what measurement or combination of measures can be used to reliably diagnose this type of hearing loss. The current study aimed to investigate the effectiveness of auditory measures that past studies have utilized for detecting HHL and/or CS.

3.3. Method

This study was approved by the research ethics committee of the University of Pretoria (HUM20190102). Informed consent were given and signed by the chief executive officer at the industry from which the test group were recruited from.

Signed informed consent forms were obtained from all participants prior to testing. A comparative within participant, cross-sectional analytic study design was implemented.

Participants

Forty participants (20 control and 20 experimental) were recruited for testing. Participants were between the ages of 18-35 years (i.e., M = 27.1 years, SD = 4.56 years). The age restriction was applied to reduce the risk of discovering age dependent changes in hearing thresholds and cognitive function (Lineweaver, Salthouse, Fristoe and Coon, 1995). Males and females were tested (20 females) and a test ear was randomly chosen for each participant. The 20 participants in the non-noise-exposed group were obtained through non-probability purposive sampling (volunteers at the University of Pretoria Speech-Language Pathology and Audiology Department). The test group were recruited from an industry where workers are exposed to occupational noise daily (non-probability purposive sampling). The non-noise-exposed group had no reported history of occupational or recreational noise exposure, whilst the test group had a minimum of two years history of occupational noise for ± 6 hours a day.

Each participant completed a noise exposure questionnaire prior to testing. The questionnaire provided the researcher with information such as participant age, gender, years exposed to occupational noise, type of hearing protection used and any ear-related problems if present.

All participants were required to present with no outer ear pathology as examined by otoscopy using a Welch Allyn pocket scope. Participants further presented with normal behavioural hearing thresholds (air conduction and bone conduction thresholds $\leq$ 20 dB HL) (Jerger and Jerger, 1980) in the frequency range between 0.125 to 8 kHz (non-noise-exposed group M PTA = 5.5, SD PTA = 4.7; test group M PTA = 7.75, SD PTA = 4.98). Pure tone testing were performed using the KuduWave 5000 by eMoyo (Pty) Ltd with insert foam tips. Absence of middle ear pathology was verified by the presence of a screening reflex at 1 kHz, a Type A

tympanogram, and the absence of an air-bone gap larger than 5 dB between air and bone conduction thresholds. Adults with a history of otologic or neurologic disease were also excluded.

Data collection

Testing took place in a quiet room for both test groups. All tests were performed on the same day at the same sitting for each participant.

Middle Ear Muscle Reflexes (MEMR)

Ipsi- and contralateral MEMR were measured in the selected ear using the Interacoustics Titan – IMP440 (Impedance module). Acoustic reflexes at single intensities of 500, 1000 and 2000 Hz were measured and a threshold was determined for each frequency by the device. Threshold was determined when a change in compliance of 0.02 ml was present at probe tone frequencies (Guest, Munro, Prendergast, et al., 2019).

Extended high frequency (EHF) audiometry

Pure tone extended high frequency air conduction audiometry was measured using the hearTest application (HearX Group, Pretoria, South Africa) installed on a Samsung Galaxy A3 smartphone. This smartphone application has been validated for the testing of extended high frequencies (Bornman et al., 2019). The smartphone was calibrated with the headphones prior to each participant being tested. Sound was conducted through circumaural sound-attenuating Sennheiser HDA200 headphone's calibrated using a plat adapter with an IEC 60318-1 G.R.A.S. Ear simulator and adhering to ISO calibration standards (ISO 389-9: 2009)**.** Participants responded through a response button on the smartphone screen each time a sound was heard. Air conduction frequencies at 10 000, 12 500 and 16 000 Hz were recorded.

Digits-in-noise test

A digits-in-noise test was performed using the hearDigits application (HearX Group, Pretoria, South Africa) installed on a Samsung Galaxy J2 smartphone. Sound was

conducted through circumaural sound-attenuating HD 280 PRO headphones. The software installed was calibrated to ISO 13485 calibration standards. Participants responded to digit triplets in noise by typing in numbers on the screen that were heard. The digits were pronounced by a female speaker with natural intonation, for example, 3–7–1. The first set of digits was presented at the participant's comfortable listening level. After responding to 25 sets of digit-triplets, a signal-to-noise ratio was calculated by the application to give an indication of the participant's word recognition abilities in noise.

Distortion product otoacoustic emission (DPOAE) test

DPOAEs were recorded using the Interacoustics Eclipse auditory evoked (AEP) response system. Using the DPOAE20, calibrated in accordance with ISO 389-9 (2014). Settings were configured at an intensity of 65 dB (L1) and 55 dB (L2) with an F2/F1 ratio of 1, 21. DPOAEs were conducted from 500 to 8000 Hz, measuring 8 points per octave. DPOAE responses were converted into half octave frequency bands to make then comparable to the audiometric frequencies.

Auditory brainstem response (ABR)

Auditory brainstem responses were recorded using the Interacoustics Eclipse EP 25 AEP system, calibrated in accordance with ISO standards for short duration stimuli (ISO 389-6: 2007). Parameters were configured for 80 dB nHL click stimuli at a rate of 27.4 Hz, with 30 – 3000 Hz filters and averaging a minimum of 4000 sweeps. Two traces using rarefaction stimulus polarity and two traces condensation polarity were measured with an artefact rejection level set at 40 µV. Participants were in a comfortable laying position with their eyes closed for the duration of the test. Reusable gold cup electrodes were prepared with Ten20 electrode paste. A two-channel electrode configuration was used. The skin was prepared with Nuprep prepping gel before placing the inverting electrode on the ipsilateral mastoid (Mi), non-inverting electrode on the high forehead (Fz), and with ground at lower forehead (Fpz). The electrode impedance was monitored and accepted once impedance was <5 kΩ or below (Crumly, 2009). An ER-3A insert earphone with soft foam ear tips was used as transducer. Wave I, III and V latencies, amplitudes and interpeak

latencies were recorded for rarefaction, condensation and alternating polarity to ensure neural synchrony and to eliminate participants that may present with auditory neuropathy spectrum disorder.

Electrocochleography (ECochG)

Electrocochleography were performed using the Interacoustics Eclipse EP 25 AEP system. Parameters were configured for click stimuli, alternating polarity, 11.3/s stimulus rate, 95 dB nHL stimulus intensity, and averaging continued until a minimum of 1500 sweeps were collected. A tympanic membrane (TM) (inverting) electrode prepared with saline solution and conductive gel was inserted inside the ear canal and placed onto the tympanic membrane. Reusable gold cup surface electrodes were prepared with Ten20 electrode paste. The skin was cleaned with Nuprep prepping gel before placement. The non-inverting electrode was placed on the on high forehead (Fz) with the ground electrode on low forehead (Fpz). A soft insert ear tip (ER-3A) was placed in the test-ear canal to conduct the stimuli and keep the TM electrode in position. Electrode impedance for surface electrodes was acceptable at $\leq$5 kΩ and for TM electrode at $\leq$20 kΩ (Crumly, 2009). The ECochG trace was repeated in order to confirm repeatability of the wave. For ECochG ratio calculation the SP/AP area ratio was measured. This was done by first marking the start of the baseline (BLst). Baseline end (BLe) was marked by the software automatically (at the next point in the waveform where the amplitude crosses the baseline). Thereafter the summating potential (SP), the beginning of the AP (AP1), action potential (AP peak) and the AP end (AP2) was marked by the researcher (Ferraro, 2011). The area ratio was automatically calculated by the software.

Analysis

Data was recorded and analysed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25)**.** Wave analysis for ABR and ECochG had to be agreed on by two experienced audiologists and where there was a difference of opinion, a third marked was asked to provide their input. Mean standard deviation (SD) and box plots were used to describe diagnostic test results. A one-way analysis of variance (ANOVA) was used to determine whether there were any statistically

significant differences between the means of the non-noise-exposed group and the noise-exposed group. For the comparison between groups for the number of absent reflexes, a difference in proportions test was used (chi-square test for homogeneity). An alpha value of $p < 0.05$ was used to indicate level of significance.

3.4. Results

In this study a comparative within participant, cross-sectional analytic study design was implemented.

Table 6 contains a summary of the mean, standard deviation and significant difference level for all audiologic tests conducted for the non-noise-exposed group (NOISE-) and noise-exposed group (NOISE+). Results that showed significant between-group differences ($p < 0.05$) are indicated through (*) at p value.

Table 6: Mean, standard deviation and significant difference level for audiologic measures for NOISE+ group and NOISE- group with significant difference indicated through (*).

		Mean (SD)				p-value
		NOISE+ group		NOISE- group		
MIDDLE EAR MUSCLE REFLEX						
MEMR		dB SPL				
	Ipsilateral					
	0.5 kHz	18	86.94 (5.98)	20	87.00 (7.33)	0.980
	1 kHz	19	90.26 (7.90)	20	86.75 (6.74)	0.143
	2 kHz	20	86.50 (5.82)	20	86.50 (5.64)	1.000
	Contralateral					
	0.5 kHz	16	93.44 (6.76)	17	86.76 (7.28)	0.010*
	1 kHz	15	95.00 (5.67)	16	89.69 (6.95)	0.027*
	2 kHz	18	89.72 (5.55)	20	88.50 (6.90)	0.554
COCHLEA						
DPOAE		Amplitude (dB SPL)				
	1 kHz	20	10.49 (5.50)	20	10.08 (5.94)	0.820
	2 kHz	20	9.52 (7.20)	20	11.20 (7.10)	0.463
	3 kHz	20	6.44 (6.79)	20	7.67 (5.09)	0.519
	4 kHz	20	4.26 (7.91)	20	7.37 (8.04)	0.225
	6 kHz	20	1.26 (6.99)	20	4.57 (8.37)	0.182
	8 kHz	20	0.09 (9.39)	20	0.16 (9.39)	0.980
		SNR (dB SPL)				
	1 kHz	20	14.72 (5.06)	20	14.96 (4.82)	0.880
	2 kHz	20	17.63 (5.62)	20	19.91 (4.45)	0.164
	3 kHz	20	17.77 (5.61)	20	19.04 (3.87)	0.408
	4 kHz	20	16.77 (5.73)	20	19.14 (5.82)	0.202
	6 kHz	20	13.89 (5.37)	20	16.49 (6.16)	0.164
	8 kHz	20	12.43 (5.59)	20	12.56 (6.20)	0.943
ECochG		Latency (ms)				

	SP	15	0.77 (0.21)	20	0.64 (0.22)	0.079
	AP Peak	15	1.59 (0.27)	20	1.41 (0.20)	0.029*
			Amplitude (μV)			
	SP	15	0.13 (0.09)	20	0.13 (0.13)	0.898
	AP	15	0.72 (0.42)	20	0.56 (0.35)	0.223
	SP/AP	15	0.18 (0.09)	20	0.22 (0.11)	0.280
			Area ratio (mV)			
	SP	15	13.09 (7.95)	20	10.61 (12.31)	0.501
	AP	15	13.69 (10.13)	20	10.53 (11.92)	0.415
	SP/AP	15	0.96 (0.41)	20	1.03 (0.50)	0.669
NEURAL PATHWAY						
ABR rarefaction polarity			Latency (ms)			
	Wave I	20	1.45 (0.18)	20	1.42 (0.15)	0.622
	Wave III	20	3.64 (0.19)	20	3.58 (0.15)	0.284
	Wave V	20	5.49 (0.19)	20	5.43 (0.26)	0.416
	Interpeak (I-III)	20	2.21 (0.21)	20	2.14 (0.21)	0.319
	Interpeak (III-V)	20	1.85 (0.14)	20	1.91 (0.14)	0.401
	Interpeak (I-V)	20	4.06 (0.25)	20	4.06 (0.25)	0.996
			Amplitude (μV)			
	Wave I	20	0.24 (0.11)	20	0.28 (0.13)	0.290
	Wave III	20	0.24 (0.11)	20	0.35 (0.20)	0.034*
	Wave V	20	0.40 (0.14)	20	0.55 (0.22)	0.014*
ABR condensation polarity			Latency (ms)			
	Wave I Latency	20	1.53 (o.25)	20	1.47 (0.18)	0.411
	Wave III Latency	20	3.72 (0.21)	20	3.62 (0.18)	0.101
	Wave V Latency	20	5.57 (0.19)	20	5.42 (0.27)	0.041*
	Interpeak Latency (I-III)	20	2.18 (0.20)	20	2.15 (0.18)	0.666
	Interpeak Latency (III-V)	20	1.85 (0.13)	20	1.80 (0.24)	0.419
	Interpeak Latency (I-V)	20	4.03 (0.25)	20	3.95 (0.24)	0.300
			Amplitude (μV)			
	Wave I	20	0.19 (0.09)	20	0.16 (0.11)	0.413
	Wave III	20	0.22 (0.10)	20	0.27 (0.16)	0.225
	Wave V	20	0.37 (0.12)	20	0.52 (0. 21)	0.008*
ABR alternating polarity			Latency (ms)			
	Wave I	20	1.48 (0.18)	20	1.43 (0.16)	0.406
	Wave III	20	3.68 (0.19)	20	3.58 (0.16)	0.069
	Wave V	20	5.49 (0.18)	20	5.42 (0.25)	0.357
	Interpeak (I-III)	20	2.21 (0.17)	20	2.15 (0.20)	0.324
	Interpeak (III-V)	20	1.81 (0.12)	20	1.85 (0.21)	0.507
	Interpeak (I-V)	20	4.02 (0.18)	20	3.99 (0.25)	0.752
			Amplitude (μV)			
	Wave I	20	0.18 (0.09)	20	0.21 (0.11)	0.475
	Wave III	20	0.21 (0.10)	20	0.29 (0.18)	0.081
	Wave V	20	0.38 (0.12)	20	0.52 (0.21)	0.018*
HIGH FREQUENCY AUDIOMETRY						
EHF audiometry			Threshold (dB HL)			
	10 kHz	20	11.50 (4.01)	20	10.50 (1.54)	0.304
	12.5 kHz	20	14.75 (10.32)	20	11.75 (5.91)	0.266
	16 kHz	20	23.00 (14.90)	20	19.00 (10.08)	0.326
SPEECH-IN-NOISE TESTING						
Digits-in-noise			SNR (dB)			
		20	-10.58 (0.97)	20	-10.79 (0.75)	0.438

(SD = standard deviation, N = number ears, p-value = calculated probability, MEMR = middle ear muscle reflex, EHF = extended high frequency, DPOAE = distortion product otoacoustic emission, SNR = signal-to-noise ratio, ABR = auditory brainstem response, ECochG = electrocochleography, dB = decibels, SPL = sound pressure level, kHz = kilohertz, ms = milliseconds, μV = microvolt, * = significant difference ($p < 0.05$))

Table 6 shows no significant between-group differences ($p > 0.05$) were measured between the NOISE+ and NOISE- group for the EHF audiometry, digits in-noise and DPOAE test. As indicated through (*) in Table 6, there were significant between-group differences measured for the MEMR, ABR and ECochG test.

Middle-Ear-Muscle-Reflex

Table 6 shows the NOISE+ group presented with a clear trend of more absent total reflexes than observed in the NOISE- group (NOISE- group = 7/120 reflexes absent, NOISE+ group = 14/120 reflexes absent). A chi-square analysis of the distribution of MEMR reflexes demonstrated they were absent in 5% of the NOISE- group and in 10.8% of the NOISE+ group. However, the difference in proportions didn't reach significance ($p = 0.094$). Figure 4 below presents the mean MEMR thresholds, comparing the NOISE- with the NOISE+ group.

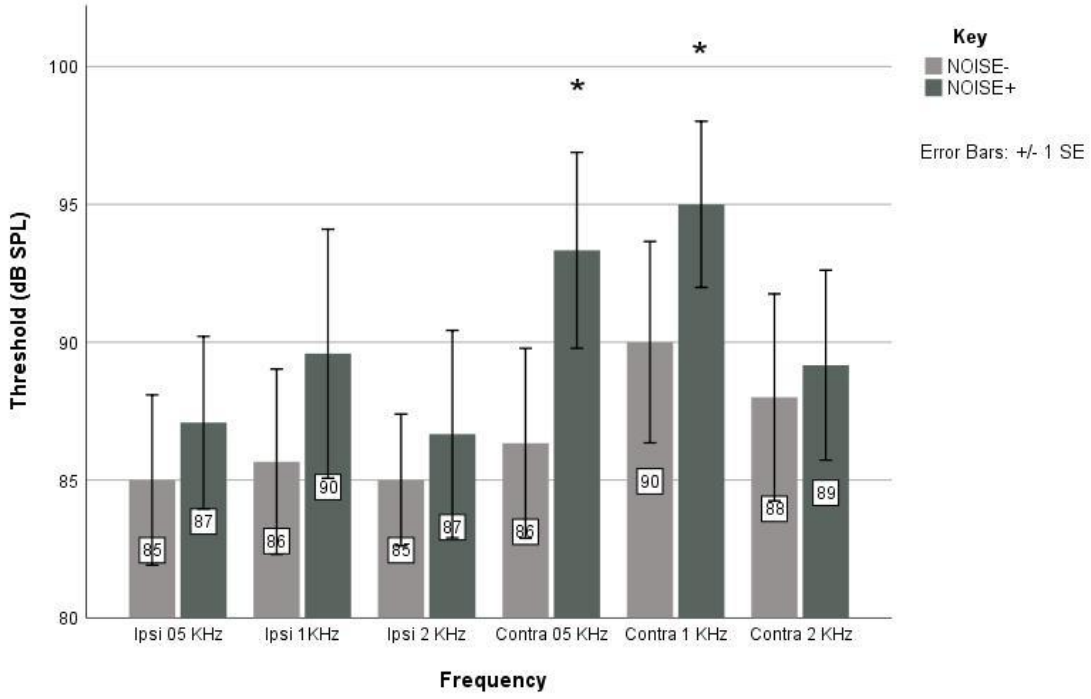

Figure 4: Mean MEMR thresholds for NOISE- group and NOISE+ group with error bars representing +/- 1 standard error

Figure 4 show the NOISE+ group presented with higher ipsi- and contralateral MEMR thresholds compared to the NOISE- group across all frequencies tested. A one-way ANOVA comparing the MEMR thresholds for NOISE- and NOISE+ groups indicated that the contralateral reflex thresholds was statistically significantly higher at 500 and 1000 Hz for the NOISE+ group ($F(1,31) = 7,421$, $p = 0.010$; $F(1,29) = 5,400$; $p = 0.027$ respectively). No significant difference was measured for the ipsilateral reflexes or at 2000 and 4000 Hz contralaterally ($p > 0.05$) between groups

Auditory brainstem response

Latency.

For ABR tested at all polarities, table 6 shows the NOISE- group presented with slightly increased wave III and V absolute latency values compared to the NOISE+ group. Data analysis showed no significant between-group difference ($p > 0.05$) for absolute or interpeak latencies of the ABR test for rarefaction or alternating polarity. Figure 5 presents the mean absolute and interpeak latencies of the ABR (condensation) test, comparing the NOISE- with the NOISE+ group.

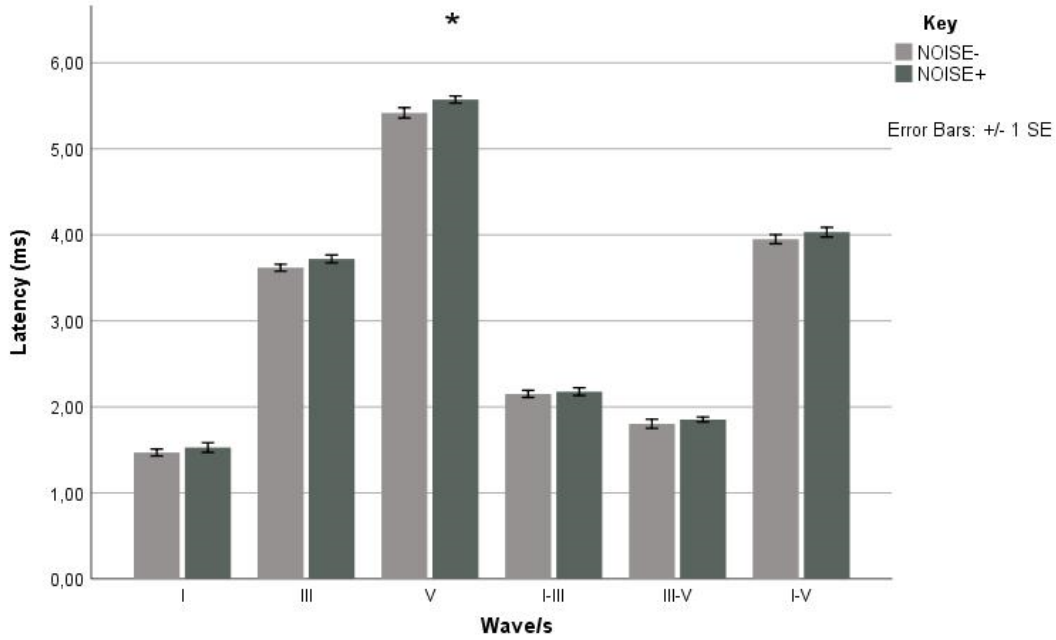

Figure 5: Mean ABR absolute and interpeak latencies (condensation polarity) for NOISE- group and NOISE+ group with standard error bars representing +/- standard error

Latencies of the ABR (condensation polarity) test for NOISE- and NOISE+ groups indicated that the wave V latency was statistically significantly later for the NOISE- group ($F(1,38) = 4{,}489$, $p = 0.041$). No significant between-group difference was measured for the absolute latencies of wave I and wave III or interpeak latencies I-III, III-V or I-V with condensation polarity ($p > 0.05$).

Amplitude.

Table 6 shows a decrease in ABR amplitudes (rarefaction polarity) for wave I, III and V in the NOISE+ group compared to the NOISE- group. Figure 6 below presents the mean amplitude responses of the ABR test rarefaction polarity, comparing the NOISE- group results with the NOISE+ group results

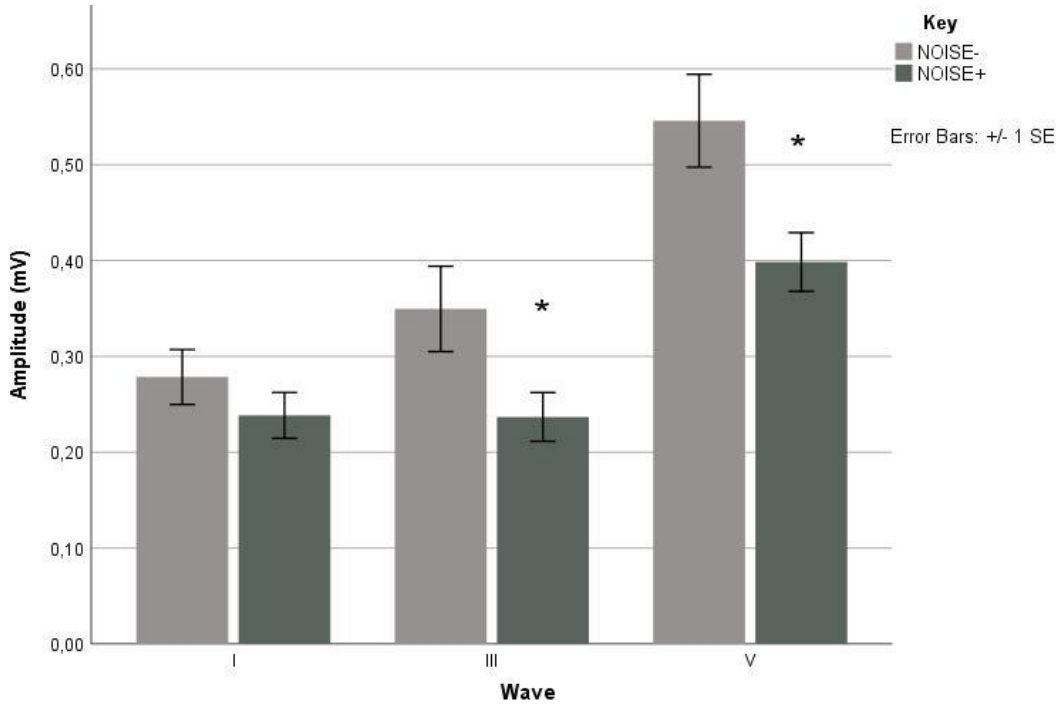

Figure 6: Mean ABR amplitudes (rarefaction polarity) for NOISE- group and NOISE+ group with error bars representing +/- standard error

ABR (rarefaction polarity) amplitudes for NOISE– and NOISE+ groups indicated that the amplitude of wave III and wave V was statistically significantly lower for the NOISE+ group ($F(1,38) = 4,834$, $p = 0.034$; $F(1,38) = 6,606$; $p = 0.014$ respectively). No significant difference was measured for the wave I amplitude response ($p > 0.05$) between groups.

For the amplitudes of the ABR using condensation and alternating polarity, the wave V amplitude was statistically significantly lower for the NOISE+ group compared to the NOISE- group ($F(1,38) = 7,835$; $p = 0.008$; and $F(1,38) = 6,114$, $p = 0.018$ respectively). No significant difference for condensation or alternating polarity was measured for the wave I or wave III amplitude response ($p > 0.05$) between groups.

Electrocochleography

Table 6 shows the NOISE+ group presented with a later mean SP latency and AP peak latency compared to the NOISE- group. A one-way ANOVA comparing the latency response of the ECochG for NOISE- and NOISE+ groups indicated that the

AP latency was statistically significantly later for the NOISE+ group ($F(1,33) = 5,182$, $p = 0.029$). No significant difference between groups was measured for the SP latency ($p > 0.05$).

Table 6 also shows the NOISE+ group mean AP amplitude was larger compared to the NOISE- group mean AP amplitude. A one-way ANOVA comparing the mean wave amplitudes for the ECochG test for NOISE- and NOISE+ groups indicated no significant difference in amplitude responses measured between groups ($p > 0.05$). The NOISE- group mean SP/AP area ratio as well as SP/AP amplitude ratio was slightly larger compared to the NOISE+ group, however no significant between-group difference in ECochG area (SP, AP or SP/AP ratio) was measured ($p > 0.05$).

3.5. Discussion

The current study utilized a number of audiologic measures that past studies advocated for the purpose of identifying HHL and/or CS. Test results from a non-noise-exposed group (NOISE- group) and a noise-exposed group (NOISE- group) were compared. The latter group would therefore be at risk for presenting with a HHL and/or. Significant between-group differences were measured for contralateral stapedial reflexes, ABR wave III and V amplitudes, ABR wave V latency, and for the AP latency of the ECochG.

MEMR and occupational noise exposure

The noise-exposed group presented with statistically higher contralateral MEMR at 0.5 kHz and 1 kHz compared to the non-noise-exposed with no reported noise exposure history ($p = 0.010$ and 0.027 respectively). Between-group differences were not significant ipsilaterally at the same frequencies.

Similar findings to the current study were observed by Valero et al. (2017) in mice with noise-induced neuropathy. Researchers measured MEMR growth functions by monitoring contralateral noise induced changes in the wideband reflectance of chirps presented to the ipsilateral ear. They discovered that the contralateral MEMR threshold was elevated and its maximum amplitude was attenuated in neuropathic

mice. On the basis hereof, Valero et al. (2017) suggested that the MEMR may be valuable in the early detection of cochlear neuropathy.

ABR wave III & V amplitude and noise exposure

A measure that has been utilized in numerous studies investigating the effects of noise exposure on human participants with normal behavioural pure tone audiometric thresholds is the ABR wave I amplitude (Bramhall et al., 2016; Grinn, Wiseman, Baker, & Prell, 2017; Grose, Buss, & Hall, 2017; Liberman et al., 2016). For the present study, one may have hypothesized that most significant differences would have been observed in the wave I amplitude of the ABR test. The amplitude of wave I was lower in the noise-exposed group than in the non-noise-exposed group, but this difference was not, however, significant ($p > 0.05$). A study conducted by Stamper, Johnson, and City (2016) observed significant ABR wave I amplitude reductions for suprathreshold alternating click stimuli in a group of 30 adults that presented with a history of noise exposure as reported on a questionnaire. The questionnaire yielded a value that was an estimate of annual amount of daily noise exposure. The participants presented with the daily noise exposure above 67 dB (A) over the previous year with majority of the noise-exposure being attributed to music listening. Bramhall et al. (2016) observed a similar association between an increased history of noise exposure and decreased ABR wave I amplitude at suprathreshold level for a population of 64 veterans who presented with normal behavioural pure tone thresholds, this time with alternating tone burst stimuli at frequencies 1, 3, 4 and 6 kHz. The noise-exposed group also reported their history of noise exposure (occupational, military and recreational) through a detailed questionnaire which divided participants into low- and high-risk of presenting with a HHL. The high risk groups presented with a calculated daily noise exposure of > 80 dB (A) over several years.

One unexpected finding by Bramhall et al. (2016) was that the group of veterans with a low risk of presenting with HHL showed similar ABR wave I amplitudes to the non-noise-exposed group with no noise exposure history. The low-risk group only used firearms during their military training rather than in combat situation. These findings

led authors to speculate that the low-risk group might have been more consistent in using adequate hearing protection in the controlled environment during training, as opposed to veterans in combat situations not being monitored on adequate hearing protection (Bramhall et al., 2016). It is therefore possible that the lack of significantly reduced wave I amplitude measurements in the current study suggests that the participants' noise exposure may have be limited by regular use of hearing protection in areas of high noise levels where they are obligated to wear hearing protection at all times

In the noise-exposed group in the present study, significantly lower wave III amplitudes for the rarefaction ABR, and significantly lower wave V amplitudes at all stimulus polarities were, however, measured compared to the non-noise-exposed group ($p < 0.05$). The Wave V amplitude reductions in the noise-exposed group contradicts the findings of Bramhall et al. (2016), Guest, Munro, Prendergast, Millman and Plack (2018) and Stamper et al. (2016), all of whom determined that the exposure to excessive noise had no effect on the ABR wave V amplitudes. Bramhall et al. (2016) further concluded that excessive noise-exposure had no effect on the ABR wave III amplitude. This was true despite the use of slower stimulus rates in the studies of Bramhall et al. (2016) (11.1/s), Guest et al. (2018) (7.05/s) and Stamper et al. (2016) (11.3/s) than in the current study, which used a rate of 27.4/s. A slower stimulus rate is associated with larger wave V amplitudes (Burkard & Sims, 2001).

Only a single study by Pushpalatha and Konadath (2016) reported significantly reduced wave III and V amplitudes as was the found in the current study. Pushpalatha and Konadath (2016) concluded that the cochlear nucleus (wave III), as well as the lateral lemniscus or inferior colliculus (wave V) in the central auditory pathway, is sensitive to neural changes caused by occupational noise exposure (Pushpalatha & Konadath, 2016). Pushpalatha and Konadath (2016) recruited participants presenting with a similar nature of noise exposure as in the current study (occupational noise experienced daily), and used a slow stimulus repetition rate of 11.1/s. Similar to the present study, the results of the occupational noise-exposed group were compared to a control group without a reported history of noise exposure.

Previous studies that did not report wave II and V reductions included participants with episodic / intermittent and recreational noise. Differences in type of noise that participants were exposed to may therefore influenced the way in which HHL presents itself - / the site of resulting auditory neural pathology. It is therefore possible that the auditory pathway structures such as the cochlear nucleus (wave III) and lateral lemniscus or inferior colliculus (wave V) may be susceptible to damage caused by a long-term noise exposure repeated on a daily, weekly, monthly or yearly basis, unlike the noise exposure that the high-risk veterans were exposed to which was intermitted (short-term) rather than chronic in nature (Bramhall et al., 2016).

In a literature review by Le Prell. (2019), the author concluded that new data obtained from animal subjects exposed to chronic (constant/long-term) noise through daily exposure paradigms are urgently needed. The author explained that the degree to which synaptic pathology or HHL will be induced by chronic noise exposure history is unknown, as this condition has not been tested in animal studies (Le Prell, 2019). Animal studies have focussed on the effects of a more intense level of noise exposure (e.g. 100 dB) for a shorter period of time (e.g. 2 hours) (Furman et al., 2013; Kujawa & Liberman, 2009; Mehraei et al., 2016), rather than investigating the effects of a lower level of chronic noise exposure (e.g. 85 dB(A)) for a longer period of time (e.g. > two years). The latter is of considerable importance since this is typical of the nature of occupational noise exposure.

ABR wave V latency and noise exposure

The wave V latency of ABR using a condensation click stimulus polarity was significantly prolonged ($p = 0.41$) for the noise-exposed group compared to the non-noise-exposed group. The wave V latency has in past studies been utilized as a clinical tool for the diagnosis of HHL and/or CS in humans (Kobel et al., 2017). Wave V latency shift has, however, mostly been observed in the presence of ipsilateral masking noise (Mehraei et al., 2016), which was not utilized in the current study.

In agreement with the current study findings, Pushpalatha and Konadath, (2016) observed a slight, but significant prolongation of the click-evoked wave V latency in a

group presenting with a history of noise exposure compared to non-noise-exposed group. Similar to the current study, their test group participants consisted of industrial workers exposed to occupational rather that recreational noise. The authors concluded that the wave V latency shift observed in noise-exposed group, may possibly be due to the pathological changes in the auditory neural pathway at brainstem level, which leads to the manifestation of a noise-induced hearing loss which may be difficult to monitor at early stages (Pushpalatha & Konadath, 2016).

As is typical of a population exposed to occupational noise, more male participants were included in the noise exposed group than females (70% male). Researchers have shown that females may present with slightly shorter (earlier) ABR wave V latencies as well as larger wave V amplitudes compared to male subjects (Jerger & Hall, 1980). It is possible, that more males being tested in the noise-exposed group contributed to the later ABR wave V latency observed in the noise-exposed group vs. the non-noise-exposed group who consisted of more female participants. This was, however, also the case in the previous study by Bramhall et al. (2016).

ECochG AP latency and noise exposure

A significantly longer ECochG AP latency was observed between the non-noise-exposed group and the noise-exposed group ($p = 0.029$). The ECochG AP latency is known to represent the ABR wave I latency (the firing of auditory nerve fibres generated by the cochlear end of the VIII th nerve) (Crumley, 2011). Table 6 showed that the noise-exposed group presented with slightly prolonged (not significant) wave I ABR latencies (rarefaction polarity mean = 1.45 ms, condensation polarity mean = 1.54 ms, alternating polarity mean = 1.48 ms).

A shift in ECochG AP latency using rarefaction and condensation clicks have been witnessed in the evaluation of individuals presenting with Meniere's disease/endolymphatic hydrops (Orchik, Ge, & Shea, 1998). It is known that long-term noise exposure can result in damage to the cochlear, but less attention has been given to the effects of long-term noise exposure to the vestibular system (Al Kindy, 2017). Researchers have found that individuals presenting with occupational

noise-induced hearing loss frequently presents with balance difficulties or symptoms resembling Meniere's disease. This lead Wu and Young (2009) to believe that long-term noise exposure may have effects on similar pathophysiological mechanisms to that of Meniere's disease (Al Kindy, 2017). The current study therefore suggests that the AP latency shift observed in the noise-exposed group may possibly be an early indicator of future equilibrium difficulties caused by noise-induced hearing loss.

Audiologic measures with non-significant between-group differences

No significant between-group difference ($p > 0.05$) was observed with digits-in-noise, extended high frequency audiometry or DPOAE test between the non-noise-exposed group and the noise-exposed group.

The most commonly expected complaint of someone presenting with neuropathic damage is difficulty understanding speech in noise (Kujawa & Liberman, 2009). In the current study no significant between-group difference was observed in the digits-in-noise results comparing the noise-exposed group with the non-noise-exposed group. Although numerous studies have failed to detect any relationship between noise history and speech-in-noise tests (Grinn et al., 2017; Prendergast et al., 2017; Yeend, Beach, Sharma, & Dillon, 2017), other studies that revealed significantly poorer speech-in-noise scores for normal hearing participants with a history of noise expose compared to participants with no noise exposure history (Hope et al., 2018; Kumar, Ameenudin, A.V Sangamanatha, & Sangamanatha, 2012). The outcomes of speech-in-noise tasks have proven to be highly dependent on specific noise task as well as participant selection criteria. Of the five studies mentioned, five different speech-in-noise tasks were utilized. In a literature review, Le Prell (2019) concluded that only studies that used the most difficult listening tasks showed greater sensitivity for detecting speech-in-noise difficulties in a noise-exposed group. Therefore, it is possible the identification of digits in noise, as was used in the current study, may not have presented participants with a sufficient level of task difficulty.

Previous research has suggested that extended high frequency audiometry is a useful tool within a clinical test battery for HHL and/or CS (Barbee et al., 2018).

Liberman et al. (2016) stated that testing audiometric thresholds at extended high frequencies was included in their study because animal studies have shown that the earliest damage from noise exposure occurs at the very basal end of the cochlea which is the area tuned to very high frequencies. These findings were also supported by Somma et al. (2008) who indicated that behavioural pure tone thresholds measured in participants presenting with a noise-induced hearing loss were substantially poorer in the extended high frequency range (9–20 kHz) compared to frequencies in the lower range (0.5–8 kHz). The researchers suggested that testing within the extended high frequency range should show the first signs of a noise-induced hearing loss and may be used to monitor individuals exposed to occupational noise daily (Somma et al., 2008). The current study, similar to Bramhall et al. (2016) who investigated the effects of occupational noise exposure on extended high frequency audiometry, showed no significant difference ($p > 0.05$) between noise-exposed group and the non-noise-exposed control group. The current findings and that of Bramhall et al. (2016) may suggest that the possible synapse loss have not regressed to cause outer hair cell damage, or that outer hair cell damage causing temporary threshold shift had fully recovered, which may be the reason why behavioural extended high frequency thresholds were not yet being effected (Liberman & Kujawa, 2018). The speculation on the lack of outer hair cell damage in the participants in the current study is consistent with lack of significance between-group differences observed in DPOAE results.

Damage to outer hair cells from noise exposure may be detected by DPOAEs in the presence of a normal behavioural pure tone thresholds, making DPOAEs one of the first tests to indicate damage due to noise (Barbee et al., 2018). Although OAEs are more sensitive in detecting noise damage than pure tone audiometry, OAEs may recover fully within twenty-four hours after noise exposure (Barbee et al., 2018). Three studies conducted on participants with behavioural pure tone thresholds within normal range also failed to observed significant differences in DPOAE measures between a control group presenting with no history of noise exposure compared to a test group with/with more history of noise exposure (Bramhall et al., 2016; Liberman et al., 2016; Prendergast et al., 2017). Failure to detect a relationship between noise

exposure history and DPOAEs were not surprising as past animal studies have shown that noise-induced auditory neuropathy resulting in temporary threshold shifts which fully recovered did not affect DPOAE (Stamper et al., 2016). These findings are also better understood by reminding oneself that the organization of the cochlear afferent innervation is of nature that 95% of cochlear afferent fibers (affected by HHL/CS) are associated with inner rather than outer hair cells (Spoendlin, 1972).

3.6. Limitations

As with previous research investigating HHL and/or CS, the amount of noise exposure that participants presented with was based on self-reported questionnaires/interviews. The present study made use of a self-compiled questionnaire to identify individuals at risk for presenting with a HHL and/or CS. All workers recruited presented with a self-reported history of high levels occupational noise exposure for at least 2 years, experienced daily. Therefore, the exact level of noise exposure the noise-exposed group presented with could not have been accurately calculated and thus were determined subjectively.

3.7. Conclusion

The current study aimed to investigate the effectiveness of auditory measures that past studies have utilized for detecting HHL and/or CS. In a sample of adults exposed to occupational noise compared to non-noise-exposed adults, significant between-group differences were measured for contralateral MEMR (500 Hz and 1000 Hz), ABR (wave V latency, wave III amplitude and wave V amplitude) and ECochG (AP latency). No significant between-group differences were detected for the speech-in-noise, extended high frequency audiometry or DPOAE tests. It was further postulated that the nature of the noise individuals are exposed to may play a role in the neural site of lesion and therefore in the effectiveness of the selected audiometric measure in identification of HHL and/or CS.

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4. SUMMARY AND CONCLUSION

The term HHL and/or CS has been used by different researches referring to varying patterns of audiometric results, patient complaints and site of lesions. The term hidden hearing loss was first explicitly defined as the selective reduction in number of synapses connecting the inner hair cells and their auditory nerve targets, resulting in a reduction of the ABR wave I amplitude (Prell, 2018). Later, the term HHL was used by Schaette and McAlpine (2011) to describe a permanent noise-induced synaptopathy and corresponding decrease in ABR wave I amplitude after the recovery of temporary threshold shifts. Lastly, the term hidden hearing loss have been extended to include functional deficits e.g. difficulty understanding speech-in-noise, tinnitus and hyperacusis whilst presenting with normal pure tone behavioural thresholds, thus the loss being 'hidden' behind a normal audiogram (Prell, 2018).

Hidden hearing loss and/or cochlear synaptopathy have shown to be challenging for both the audiologist and the patient. Patients may seek help with complaints of tinnitus, hyperacusis and inability to understand speech in noise, only to find out that conventional behavioural audiometric testing does not validate what they are experiencing. Clinicians are left feeling helpless due to inability to diagnose or treat the patient's symptoms (Barbee et al., 2018). There is little direct evidence of a noise-induced neuropathy in humans similar to that witnessed in rodent studies (Plack et al., 2014). There is, however, evidence that an individual with a history of excessive noise exposure may show deficits in complex discrimination tasks, despite presenting with near-normal threshold sensitivity (Plack et al., 2014).

It has been determined that a reduction of inner hair cell synapses connected to the auditory nerve is symptomatic of a HHL and/or CS (Prell, 2018), and that this selective neural loss affects a sub-group of nerve fibres with low spontaneous rates and high thresholds (Furman et al., 2013). With this information, past studies have used a combination of both electrophysiological and behavioural approaches, aiming to detect HHL and/or CS in humans (Kobel et al., 2017). To date there is no consensus on a single clinical measure or combination of measures that are a

reliable indicators for the diagnosis of HHL and/or CS as past studies has had varying outcomes (Mehraei et al., 2016).

The current study therefore examined the utility and effectiveness of auditory measures to identify HHL and/or CS. This was done by comparing several audiologic test results between a group of adults exposed to occupational noise and therefore at risk of presenting with a HHL and/or CS (noise-exposed group) and a group of adults without a history of reported noise exposure (non-noise-exposed group). Audiologic tests included for the test battery were extended high frequency pure tone audiometry, MEMR, ABR, ECochG and a digits-in-noise test.

4.1. Summary of study findings

The current study detected significant between-group differences in test results for the following auditory measures: contralateral stapedial reflexes, ABR wave III and V amplitudes, ABR wave V latency, and for the AP latency of the ECochG.

For the MEMR, contralateral stapedial reflexes measures at 0.5 Hz and 1 kHz were significantly elevated for the noise-exposed group compared to the non-noise-exposed group. Similar contralateral threshold elevations has been observed in mice (Valero et al., 2017), but have not been reported in human studies. A single study failing to detect a relationship between HHL and/or CS and MEMR thresholds, included the measurement of ipsilateral reflexes only but not contralateral reflexes, as was found to be pertinent in the current study (Guest, Munro, & Plack, 2019).

A measure that has been utilized in numerous studies investigating the effects of noise exposure on human participants with normal behavioural pure tone audiometric thresholds is the ABR wave I amplitude. For the present study, the amplitude of wave I was lower in the noise-exposed group than in the non-noise-exposed group, but this difference was not significant. Similarly, the AP amplitude of the ECochG was higher, but not statistically for noise-exposed compared to non-noise-exposed individuals. Significant between-group differences were however detected for the ABR wave III and V amplitudes, and for the ABR wave V latency. Only one study by Pushpalatha and Konadath (2016) reported similar findings (significantly reduced wave III and V

amplitudes, as well as significantly later wave V latencies) in a noise-exposed group compared to a non-noise-exposed group of participants all of whom presented with normal behavioural pure tone thresholds. Similar to the current study, their noise-exposed group consisted of industrial workers exposed to occupational, rather than recreational noise, or a combination of both (Pushpalatha & Konadath, 2016). Other studies that did not find significant reductions in waves III or V but rather in wave I amplitude reported on individuals with estimates of lifetime noise exposure based on impulse noise exposure and/or recreational noise, and not necessarily occupational noise exposure. Given that the current study's findings suggest a more central rather than peripheral site of lesion along the auditory neural pathway, it was therefore suggested that the nature of the noise individuals are exposed to may play a role in the neural site of lesion in hidden hearing loss and/or cochlear synaptopathy, and therefore in the choice of audiometric test measure.

Lastly, a significantly longer ECochG AP latency was observed for the noise-exposed group compared to the non-noise-exposed group. The ECochG AP latency is known to represent the ABR wave I latency (the firing of auditory nerve fibres generated by the cochlear end of the VIII th nerve) (Crumley, 2011). The longer ECochG AP latencies were in correlation with slightly longer, however not significant, ABR wave I latencies observed in the noise-exposed group.

No significant between-group difference was observed with digits-in-noise, extended high frequency audiometry or DPOAE test between the non-noise-exposed group and the noise-exposed group.

4.2. Clinical implications

- **Inclusion of contralateral MEMR, ABR and ECochG may be an appropriate combination of measures for the purpose of identifying HHL and/or CS**

As the measurement of MEMR are readily available in all audiological clinics, the inclusion hereof for further investigating adults with normal behavioural pure tone thresholds may be an objective and time-efficient addition to identify possible HHL and/or CS.

However, despite significant between group differences in test results, identification of HHL and/or CS cannot be achieved by a single measure, but perhaps postulated on the basis of a test battery that includes MEMR, ABR and ECochG.

- **Importance/impact of hearing protection**

A study conducted by Bramhall et al. (2016) compared the ABR wave I amplitude results between a non-noise-exposed group and three groups varying in the extend of noise-exposure (veterans with a high noise exposure history, veterans with a low noise exposure history and non-veterans with a history of fire-arm use). ABR wave I amplitude reductions were observed in the group of veterans presenting with a high noise exposure history as well as in the group of non-veterans presenting with a history of fire-arm use compared to a non-noise-exposed group.

Surprisingly, the low-risk group of veterans showed similar ABR wave I amplitude results as observed in the non-noise-exposed group. It was learned that the low-risk veterans only used fire-arms in military training rather than in combat situation. Thus these low-risk veterans were always in a controlled environment where they were monitored on wearing adequate hearing protection whilst using fire-arms. The lack of wave I amplitude reduction reported in the current study is therefore consistent with findings by Bramhall et al. (2016) in the low-risk group, suggesting that participants' noise exposure may be limited by regular use of hearing protection in areas of high noise levels where workers are obligated to wear hearing protection at all times

These findings highlight the important role of hearing protection in an occupational setting for the purpose of not only reduction of temporary and permanent threshold shifts, but also for the prevention of HHL.

4.3. Critical evaluation

It is important to interpret the present study findings within the framework of study strengths and limitations. This helps the researcher to evaluate the usefulness and validity of the research results.

4.3.1. Study strengths

- All noise-exposed participants were recruited from the same industry, all presenting with a history of noise exposure similar in nature. This study strength allowed the researcher to draw conclusions regarding the effect of difference in duration and nature of noise exposure on the auditory system. This study strength therefore minimized the variability of nature of noise exposure across the participant group, compared to previous studies who investigated an estimated amount of lifetime noise exposure.
- Furthermore, a study strength was that multiple measures were conducted in one sitting, on the same day. This eliminated the risk of changes in auditory status (e.g. change in middle ear recordings) if data were to be obtained over several days. A within participant study design reduced the risk of errors associated with individual differences as participants were not randomly assigned to groups, but had to adhere to a inclusion criteria.
- The current study made use of a broad battery of audiometric measures that have previously been associated with HHL and/or CS.
- A limited age range was used in participant selection so that the effect of noise exposure on hidden hearing loss could be identified independently from an age related hearing loss/pathology. Age related changes to the auditory system can affect both the inner and outer hair cells found in the cochlea, afferent neural fibres and the stria vascularis (Ferrite & Santana, 2005).

4.3.2. Study limitations

- In the current study, as was the case with all previous studies investigating HHL and/or CS, there is no consensus/agreement on what HHL and/or CS in humans are defined as. In addition, although the participants were exposed to

occupational noise and at risk of presenting with HHL and/or CS, as is often reported in literature, it was not known for sure they did indeed present with it.

- One of the greatest variables in studies investigating HHL and/or CS is the noise history that participants presents with. Past studies have either used a formula to calculate an estimate of lifetime noise exposure and/or made use of a self-reported noise history questionnaire or interview. The present study made use of a self-compiled questionnaire to identify individuals at risk for presenting with a HHL and/r CS and were recruited from an industry where noise conservation program was in place due to known risk for developing noise-induced hearing loss. All workers recruited presented with a self-reported history of high levels occupational noise exposure for at least two years, experienced daily. As with other studies, the exact level of noise exposure that the noise-exposed group presented with was not measured objectively.
- This study further did not account for the effects of gender on the ABR test results. Seventy present of the non-noise-exposed group were female participants, compared to only 30% of the noise-exposed group being female. It has been reported that females may present with slightly shorter (earlier) ABR wave V latencies as well as larger wave V amplitudes compared to male subjects (Jerger & Hall, 1980). It is a possibility that more males being tested in the noise-exposed group contributed to the later ABR wave V latency and larger wave V amplitude observed in the noise-exposed group compared to the non-noise-exposed group who consisted of more female subjects.

4.4. Future research

- The current study postulated that the nature of the noise exposure that humans are exposed to may be related to the site of lesion of HHL and/or CS. Animal studies investigating the effects of a noise exposure similar to the nature of occupational noise (constant/long-term noise exposure experienced for days, months and years) are urgently needed, to better understand various findings that have thus far been observed in individuals with a history of

constant/long-term noise exposure (Le Prell, 2019). Past animal studies have focussed on the effects of an intense level of noise exposure (e.g. 100dB) for a shorter period of time (e.g. 2 hours) (Furman et al., 2013; Kujawa & Liberman, 2009; Mehraei et al., 2016), rather than investigating the effects of a lower level of chronic noise exposure (e.g. 85 dB(A)) for a longer period of time (e.g. > two years). With regards to studies conducted on human participants, this study suggests that different natures/types of noise-exposure may have an influence on the neural site of lesion of HHL and/or CS on the auditory system. It is therefore suggested that future research be conducted on specific noise exposed groups (e.g. occupational, fire-arm use, music listening) and not, as observed in many past studies, on a wide variety of calculated life-time noise exposure including numerous natures of noise exposure.

- It is recommended that studies be conducted on gender-matched participants. The inclusion of more females in the non-noise-exposed group may have resulted in an ABR wave V latency difference observed between groups.
- The ultimate goal for future research will be to establish diagnostic norms to clinically be used for the diagnosis of hidden hearing loss, or at least norms that suggest an individual is at risk of presenting with HHL. If this is at all possible to establish such clinical norms are made available in future, diagnosed individuals can be provided with the treatment they need which may vary from management strategies.

4.5. Conclusion

The current study aimed to investigate the effectiveness of auditory measures that past studies have utilized for detecting HHL and/or CS. In a sample of adults exposed to occupational noise compared to non-noise-exposed adults, significant between-group differences were measured for contralateral MEMR (500 Hz and 1000 Hz), ABR (wave V latency, wave III amplitude and wave V amplitude) and ECochG (AP latency). Results suggested that the inclusion of these three measures

may be valuable in a test battery investigating HHL and/or CS in populations presenting with a noise exposure history similar to the nature of occupational noise accompanied by unexplained hearing difficulties. No significant between-group differences were detected for the speech-in-noise, extended high frequency audiometry or DPOAE tests. It was further postulated that the nature of the noise individuals are exposed to may play a role in the neural site of lesion and therefore in the effectiveness of the selected audiometric measure in identification of HHL and/or CS.

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6. APPENDICES

Appendix A

Ethical Clearance Form: Faculty of Humanities

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Humanities 100.
1919 - 2019

Research Ethics Committee

8 February 2019

Dear Ms Pienaar

Project:	**Sensitivity of audiologic measures to hidden hearing loss**
Researcher:	**A Pienaar**
Supervisors:	**Prof L Pottas and Dr L Biagio De Jager**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**15204652 (HUM20190102)**

Thank you for the application that was submitted for ethical consideration.

I am pleased to inform you that the above application was approved by the Research Ethics Committee at the meeting held on 31 January 2019. Data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should your actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: PGHumanities@up.ac.za
cc Prof L Pottas and Dr L Biagio De Jager (Supervisors) Prof J van der Linde (HoD)

Appendix B

Letter of Permission: Chief Executive Officer Industry

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Department of Speech-Language Pathology and Audiology
Lynnwood Rd, Hatfield, Pretoria, 0002
Andrea Pienaar, Researcher
Tel. nr: 0813271143

Dear Sir/Madam,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY AT YOUR INDUSTRY

I, Andrea Pienaar, will be doing my Master's degree in Audiology in 2019. I hereby request permission to conduct my research study at your industry. If permission is granted, I intend to start with the data collection for the aforementioned from January 2019.

The title of my study: The Sensitivity of Audiological Measures to Hidden Hearing Loss

Cochlear synaptopathy is known as a hidden hearing loss due to the fact that the standard audiologic test battery (hearing test) is not able to detect this type of hearing loss. The leading cause of such a neural loss is exposure to noise, aging and the combination of these two factors. The aim of this study is to detect which test or combination of tests conducted on employees are the most sensitive to this type of hearing loss.

I am approaching your company as your employees are exposed to occupational noise on a daily basis. Therefore, they are at risk of developing hidden hearing loss.

This study will benefit employees as they will receive a complete hearing assessment. After identifying hidden hearing loss in certain employees, they may finally understand why they struggle to hear in noisy situations even though they pass their annual hearing screen each year.

I will also be willing to explain this type of hearing loss to your employees before the study through a short presentation. This will be for them to comprehend how important it is to use hearing protection in the workplace and what affects this hearing loss has in daily living.

Before granting permission for employees to partake in this study, you should fully understand what this study entails. We therefore encourage you to read the following information before granting permission.

Volunteers

Participants will consist of your employees. These participants will be of any gender and their ages should range from 18-50 years.

Purpose

The purpose of this study is to examine the effectiveness of auditory measures that past studies have proven to have potential use in a clinical test battery for identifying a hidden hearing loss and/or cochlear synaptopathy.

Procedures

Various tests will be on conducted on each participant. These tests will range from behavioural tests (such as a questionnaire, responding to sounds, listening in noise etc.) to objective tests (that do not require any responses from employee).

Due to the fact that employees will be receiving a comprehensive hearing assessment that tests various aspects of auditory and neural functioning, it may take

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Hatfield 0028, South Africa
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approximately two hours per employee. For this reason I do recommend that we do all testing at your premises to minimize time taken off work.

As mentioned above, these tests may greatly impact your employees in order to understand their possible hearing difficulties.

Rights as a volunteer

Your employees' participation in this study is voluntary. Should they wish to withdraw from this study, they are welcome to do so at any stage without any negative consequences.

Confidentiality

All information and data obtained will be kept confidential. They will be assigned a number and no identifying information will be disclosed during any part of data collection or publication of results.

Risks and benefits

Employees are at minimal risk as these tests are not invasive. None of the tests performed during this study are harmful to the auditory system. Participants will benefit from this study by obtaining a comprehensive hearing evaluation.

Data storage

Data will be stored at the University of Pretoria - Department of Speech-Language Pathology and Audiology, Communication Pathology Building, Lynnwood Rd, Hatfield, Pretoria for 15 years for research and archiving purposes.

Should you require any additional information or clarification regarding the above, you are welcome to contact me.

University of Pretoria, Private Bag X20

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UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

My contact details are:

E-mail address: andreapienaar40@gmail.com

Cell number: 082 327 1143

Thank you for considering this request

Kind regards, Andrea Pienaar

Head: Department of Speech- Language Pathology and Audiology

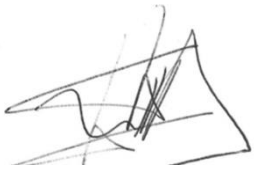
Dr. Jeannie van der Linde

E-mail: jeannie.vanderlinde@up.ac.za

Supervisor

Dr. Leigh Biagio de Jager

leigh.biagio@up.ac.za



Co-supervisor

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Prof. Bart Vinck

E-mail: bart.vinck@up.ac.za

Informed consent regarding participation in the research project

We, HENRY WESSENSEE, hereby consent to participate and provide previous audiological data of our employees to the research project entitled "Sensitivity of audiologic measures to cochlear synaptopathy", undertaken by Andrea Pienaar in fulfilment of the requirements of MA (Audiology). We have read and understood the information above and have been given opportunities to ask the researcher questions in order to obtain clarification of any aspect of the study.

We understand that participating in this research project is voluntary and that we may withdraw from participation at any point without any negative consequences.

Industry manager

2018/11/09

Date

AEROSUD
Aviation
Co Reg No: 1990/005814/07
VAT No: 4630116657
PO Box 60675
Pierre van Ryneveld, 0045
Tel No: 012 662 5000
Fax No: 012 662 5181
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Appendix C

Letter of Informed Consent: Noise-exposed group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Department of Speech-Language Pathology and Audiology

Lynnwood Rd, Hatfield, Pretoria, 0002

Andrea Pienaar, Researcher

Tel. nr: 0813271143

Dear Sir/Madam

Re. Information form regarding participation in the research study

Thank you for considering taking part in this research study. This study is aims to determine the effectiveness of auditory measures for detecting hidden hearing loss and/or cochlear synaptopathy. This study is being completed in fulfilment of the requirements of the degree Master of Arts (Audiology).

We encourage you to read the following letter before agreeing to participate.

Volunteers

Should you wish to participate in this study you should:

- Be between the ages of 18–50 years
- Be proficient in English
- Have normal hearing as far as you are aware
- No ear-related infections or pathologies as far as you are aware
- No neurologic disease as far as you are aware

Purpose

The purpose of this study is to examine the effectiveness of auditory measures that past studies have proven to have potential use in a clinical test battery for identifying a hidden hearing loss and/or cochlear synaptopathy.

Procedures

During this study a number of tests will be conducted. Some of these tests will require you to respond to sound stimuli and other tests will not require any responses. The tests will be conducted at your workplace to minimize time taken off work, as testing may take up to two hours per participant.

Should you agree to participate; an audiological test battery will be conducted. The test battery will include:

- Otoscopy (examination of outer-ear)
  Otoscopy is a physical examination of the outer-ear. The participant will be required to sit still whilst the researcher examine his/her ear canal with a light.
- Pure tone audiometry (examination of your hearing abilities)
  Pure tone audiometry requires the participant to sit in a sound proof booth with headphones on his/her ears. The participant will be asked to respond (push of a button) to sounds being presented through the headphones by the researcher. Sounds will vary from high to low sounds as well as different pitches of sounds.
- Tympanometry (examination of middle-ear)
  During tympanometry the participant will be required to sit still whilst a probe is placed in the ear-canal. The test does not require active participation from the participant.

Based on the above mentioned test results you may or may not then undergo further

tests:

- DP-otoacoustic emission test (examination of inner-ear)

  DP-otoacoustic emission testing requires the participant to sit still whilst a probe is placed in the ear-canal. The participant will hear sounds ranging in loudness and pitch. No active participation is required from the participant.
- Extended high-frequency audiometry (examination of hearing abilities at higher pitches)

  During extended high-frequency audiometry the participant will sit in a sound proof booth with headphones on his/her ears. He/she will again be asked to respond to sounds being presented by the researcher. The sounds will be at presented at high pitches.
- Auditory brainstem response (examination of neural pathway up to brainstem)

  During auditory brainstem response testing the participant will be asked to lay down/sit comfortably for the duration of the test. Electrodes will be placed behind both ears as well as on his/her forehead. No active participation will be required from the participant. The participant will be asked to minimize movement as much as possible.
- Electrocochleography (examination of neural integrity)

  During electrocochleography testing participants will be asked to lay down/sit comfortably for the duration of the test. Electrodes will be placed in the participant's ear canal as well as on his/her forehead. No active participation will be required from the participant.
- Speech-in-noise test (examination of hearing performance in presence of noise)

  The participant will be asked to listen and repeat digits presented through headphones by the researcher. Digits presented will vary in loudness and

pitch.

Rights as a volunteer

Your participation in this study is voluntary. Should you wish to withdraw from this study you are welcome to do so at any stage without negative consequences.

Confidentiality

All information and data obtained will be kept confidential. No Identifying information will be disclosed during the data collection or publication of this study as a number will be allocated to each participant. Data will be reported anonymously

Risks and benefits

You are at minimal risk as the tests are not invasive. None of the tests performed during this study are harmful to the auditory system. You will benefit from this study by obtaining a comprehensive hearing evaluation free of charge. If your test results indicate cochlear synaptopathy, you may gain comprehension of why your annual hearing test indicate normal hearing, but you struggle to understand speech in noisy situations. You are welcome to withdraw from this study at any time with no negative consequences.

Data storage

Data will be stored at the University of Pretoria - Department of Speech-Language Pathology and Audiology, Communication Pathology Building, Lynnwood Rd, Hatfield, Pretoria for 15 years for research and archiving purposes.

Should you require any additional information, or clarification of the above mentioned information, feel free to contact Andrea Pienaar at 081 327 1143.

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YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Should you wish to participate in this study please complete the informed consent form below.

Andrea Pienaar

Researcher

Head: Department of Speech- Language Pathology and Audiology

Dr. Jeannie van der Linde

Supervisor

Dr. Leigh Biagio de Jager

Co-supervisor

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Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Department of Speech-Language Pathology and Audiology
Lynnwood Rd, Hatfield, Pretoria, 0002
Andrea Pienaar, Researcher
Tel. nr: 0813271143

INFORMED CONSENT FORM

Thank you for showing interest in this research project.

Please complete the following:

The researcher has explained to me what this study entails.

I,_____ (name and surname), hereby voluntarily consent to participate in this study - Sensitivity of audiologic measures to hidden hearing loss. I am aware that this data will be used for research purposes only. I am aware that I may withdraw from this project at any time should I wish to do so. I am further aware that I have the opportunity to ask questions at any point during the study if I have any uncertainties.

_____ _____

Signature **Date**

Appendix D

Letter of Informed Consent: Non-noise-exposed group

Department of Speech-Language Pathology and Audiology
Lynnwood Rd, Hatfield, Pretoria, 0002
Andrea Pienaar, Researcher
Tel. nr: 0813271143

Dear Sir/Madam

Re. Information form regarding participation in the research study

Thank you for considering taking part in this research study. This study is aims to determine the effectiveness of auditory measures for detecting hidden hearing loss and/or cochlear synaptopathy. This study is being completed in fulfilment of the requirements of the degree Master of Arts (Audiology).

We encourage you to read the following information before agreeing to participate.

Volunteers

Should you wish to participate in this study you should:

- Be between the ages of 18–50 years
- Be proficient in English
- Have normal hearing as far as you are aware
- No ear-related infections or pathologies as far as you are aware
- No neurologic disease as far as you are aware

Purpose

The purpose of this study is to examine the effectiveness of auditory measures that

past studies have proven to have potential use in a clinical test battery for identifying a hidden hearing loss and/or cochlear synaptopathy.

Procedures

The procedures will be conducted at the Department of Speech-Language Pathology and Audiology at the University of Pretoria. Should you agree to participate; an audiological test battery will be conducted. The test battery will include:

- Otoscopy (examination of outer-ear)
  Otoscopy is a physical examination of the outer-ear. The participant will be required to sit still whilst the researcher examine his/her ear canal with a light.
- Pure tone audiometry (examination of employees hearing abilities)
  Pure tone audiometry requires the participant to sit in a sound proof booth with headphones on his/her ears. The participant will be asked to respond (push of a button) to sounds being presented through the headphones by the researcher. Sounds will vary from high to low sounds as well as different pitches of sounds.
- Tympanometry (examination of middle-ear)
  During tympanometry the participant will be required to sit still whilst a probe is placed in the ear-canal. The test does not require active participation from the participant.

Participants will be selected based on the aforementioned test results and will then undergo further tests:

- DP otoacoustic emission test (examination of inner-ear)
  DP-otoacoustic emission testing requires the participant to sit still whilst a probe is placed in the ear-canal. The participant will hear sounds ranging in loudness and pitch. No active participation is required from the participant.

- Extended high-frequency audiometry (examination of hearing abilities at higher pitches)

  During extended high-frequency audiometry the participant will sit in a sound proof booth with headphones on his/her ears. He/she will again be asked to respond to sounds being presented by the researcher. The sounds will be at presented at high pitches.
- Auditory brainstem response (examination of neural pathway up to brainstem)

  During auditory brainstem response testing the participant will be asked to lay down/sit comfortably for the duration of the test. Electrodes will be placed behind both ears as well as on his/her forehead. No active participation will be required from the participant. The participant will be asked to minimize movement as much as possible.
- Electrocochleography (examination of neural integrity)

  During electrocochleography testing participants will be asked to lay down/sit comfortably for the duration of the test. Electrodes will be placed in the participant's ear canal as well as on his/her forehead. No active participation will be required from the participant.
- Speech-in-noise test (examination of hearing performance in presence of noise)

  The participant will be asked to listen and repeat digits presented through headphones by the researcher. Digits presented will vary in loudness and pitch.

<u>Rights as a volunteer</u>

Your participation in this study is voluntary. Should you wish to withdraw from this

study you are welcome to do so at any stage without negative consequences.

Confidentiality

All information and data obtained will be kept confidential. No Identifying information will be disclosed during the data collection or publication of this study as a number will be allocated to each participant.

Risks and benefits

You are at minimal risk as the tests are not invasive. None of the tests performed during this study are harmful to the auditory system. You will benefit from this study by obtaining a comprehensive hearing evaluation. You are welcome to withdraw from this study at any time with no negative consequences.

Data storage

Data will be stored at the University of Pretoria - Department of Speech-Language Pathology and Audiology, Communication Pathology Building, Lynnwood Rd, Hatfield, Pretoria for 15 years for research and archiving purposes.

Should you require any additional information, or clarification of the above mentioned information, feel free to contact Andrea Pienaar at 081 327 1143.

Should you wish to participate in this study please complete the informed consent form below.

Andrea Pienaar

Researcher

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Head: Department of Speech- Language Pathology and Audiology

Dr. Jeannie van der Linde

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INFORMED CONSENT FORM

Thank you for showing interest in this research project.

Please complete the following:

The researcher has explained to me what this study entails.

I,_____ (name and surname), hereby voluntarily consent to participate in this study – Sensitivity of audiologic measures to hidden hearing loss. I am aware that this data will be used for research purposes only. I am further aware that I may withdraw from this project at any time should I wish to do so.

_____ _____

Signature **Date**

Appendix E

Participant Questionnaire: Health and Noise exposure

Noise exposure history questionnaire

Please answer the following questionnaire as completely and accurately as you can. All information provided will be kept confidential.

Age: _____ Gender: _____

Occupation: _____ Date: _____

Participant Number: _____

Noise Exposures:

1. Are you/have you been exposed to loud occupational noise at your current/past job? Yes No
   Average hours/day:

2. Do you regularly engage in noisy hobbies such as power tools, firearms, loud music or use of motorcycles? Yes No
   If yes, please describe:

Additional information:

Yes No I struggle to understand words in everyday speech

Yes No I experience tinnitus (ringing in my ears)

Yes No I am sensitive to loud sounds

Do you have a history of otologic disease (earache, ear infection, ear-pain, ear

deformities etc.)? Yes No

If yes, please specify:

Do you have a history of neurologic disease (Epilepsy, Alzheimer's, dementia, migraines, tumours, etc.)? Yes No

If yes, please specify: