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Auditory neural function of normal hearing adults with Type 2 Diabetes Mellitus

by

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ABSTRACT

Background: The prevalence of diabetes mellitus is growing worldwide. Type 2 Diabetes Mellitus (T2DM) can lead to damage to various organs by affecting the intricate nerve and blood vessel systems in the body caused by hyperglycaemia, including the auditory neural pathway.

Purpose: This study aimed to assess the auditory neural function of adults with T2DM by means of Auditory Brainstem Responses (ABR) with various stimulation rates, presenting with normal behavioural audiometric thresholds.

Research Design: Cross-sectional comparative study of ABR latencies and amplitudes and the impact of various stimulation rates in T2DM participants when compared to gender and age-matched controls without diabetes.

Study Sample: Sixty participants, thirty with T2DM and 30 without T2DM were recruited and gave informed consent. The thirty T2DM participants aged 20-60 years were recruited from three clinics including two private and one public tertiary clinic. The control group consisted of thirty healthy age and gender-matched volunteers. Behavioural audiometry was performed to ensure a normal pure tone average (< 25 dB HL).

Data collection and analysis: The Interacoustics Eclipse Auditory Evoked Potentials (AEP) system was used for the ABR measures which were analysed using linear mixed models. Data consisted of latencies and amplitudes of wave I, III and V and interpeak latencies of I-III, III-V and I-V of the 31.1 Hz rate. Wave V latencies and amplitudes for the 45.1 and 61.1 Hz stimulation rates were also measured.

Results: Wave III latency at 31.1 was significantly delayed in those with T2DM compared to the control group ($p<0.05$). Participants with T2DM presented with prolonged wave V latencies at the faster stimulation rates than those without T2DM, but the shift was not statistically different between groups. Diabetes status had no moderating effect of wave V latency at the different stimulation rates.

Conclusion: The results identified that the rate study was not affected by any confounding variables such as diabetes status and glucose level. However, the subclinical neurophysiological pathology, specifically at the level of the brainstem, as demonstrated by the delay in wave III, may be at least part of the reason for complaints relating to bilateral hearing difficulties in noise

Keywords: Diabetes Mellitus, Type 2 Diabetes Mellitus, Auditory Brainstem Response, rate study, Auditory neural

LIST OF ABBREVIATIONS

ABR	Auditory Brainstem Response
AEP	Auditory Evoked Potentials
daPa	Dekapascal
dB HL	Decibel Hearing Level
dB nHL	Decibel normal Hearing Level
dB SPL	Decibel Sound Pressure Level
DM	Diabetes Mellitus
FPG	Fasting Plasma glucose
Fpz	Midline Low Forehead
Fz	Midline High Forehead
Hz	Hertz (frequency)
IQR	Inter-Quartile Range
kOhm	Kilohm
M1	Mastoid left
M2	Mastoid right
µV	Microvolt
mmol/L	Millimoles per litre
ml	Millilitre
ms	Milliseconds
OGTT	Oral Glucose Tolerance Test
peSPL	peak equivalent Sound Pressure Level
PTA	Pure Tone Average
SD	Standard deviation
T2DM	Type 2 Diabetes Mellitus
TM	Tympanic Membrane

FORMATTING:

APA referencing style 6th edition was used in this dissertation

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CHAPTER 1

INTRODUCTION

CHAPTER 1: INTRODUCTION

1.1. Diabetes Mellitus related complications

Diabetes Mellitus is a common metabolic disease which results in numerous medical complications due to damage, dysfunction and failure of various organs (American Diabetes Association (ADA), 2014; de David, Finamor, & Buss, 2018). Diabetes Mellitus cases can be distinguished into two broad subtypes depending on the cause of excess glucose in the bloodstream, otherwise known as hyperglycaemia (American Diabetes Association (ADA), 2014).

Type I Diabetes Mellitus, also known as insulin-dependent diabetes, is caused by a deficiency of insulin secretion by the beta cells in the pancreas (de David et al., 2018). The second and most common is Type 2 Diabetes Mellitus (T2DM), also previously referred to as non-insulin-dependent diabetes. Metabolic control for those with T2DM can usually be achieved by proper diet, physical exercise and use of accompanying oral hypoglycemic agents in severe cases (de David et al., 2018). This subtype is caused by insulin resistance of the peripheral cells, insulin secretion deficiency or a combination of both (ADA, 2014; de David et al., 2018; Martin et al., 1992).

According to the International Diabetes Federation (IDF) (2017) 425 million people were living with diabetes in 2017 with an estimated increase of up to 629 million by 2045. In addition to this, the number of South African adults living with DM is estimated to rise from 5.4% to 6.1% in the same time frame (IDF, 2017). The increase of population size, urbanization, age, obesity and lower physical activity has led to a higher prevalence of diabetes mellitus within South Africa, adding to the global burden of disease (Hlayisi, Petersen, & Ramma, 2018; Wild, Roglic, Green, Sicree, & Hilary, 2004). However even with these growing numbers, there is still a high level of uncertainty of the statistics- as an estimated 84.8% of South Africans remain undiagnosed, and more alarmingly, untreated (Cardiovascular Diabetes Education (CDE), 2016; Hlayisi et al., 2018). These current statistics suggest concerns for both hearing healthcare practitioners and the South African health system as the association between DM and hearing loss, with on-going discussion about the configuration and degree thereof, causes a higher need for early identification and proper treatment in addition to existing health-related issues of T2DM (Calvin & Watley, 2015; Hlayisi, Petersen, & Ramma, 2018; Hong, Buss, & Thomas, 2013; Karabulut et al., 2014; Krishnappa & Naseeruddin, 2014; Mitchell et al., 2009).

The majority of DM studies focus on hyperglycaemia as the leading cause for angiopathy, also known as a disease of the blood vessels (Fowler, 2008). Angiopathy associated with diabetes causes macro- and microvascular complications. Macrovascular complications

include arterial walls narrowing which leads to complications such as heart disease (ADA, 2014; de David, Finamor, & Buss, 2018; Fowler, 2008). Microvascular complications, or damage to small blood vessels, lead to retinopathy (eyes), nephropathy (kidneys), peripheral and autonomic neuropathy which includes the nervous system (ADA, 2014; de David et al., 2018; Hlayisi et al., 2018). This effect on the intricate nerve and blood vessel system in the body could lead to a higher possibility of more organs being affected by DM, not only those with more visible symptoms such as the auditory system (de David et al., 2018). This increases the chances of those with T2DM to develop hearing impairment throughout their lives in addition to any other medical implications.

1.2. Effects of Type 2 Diabetes Mellitus on the auditory system

The reason for the degeneration of the auditory function in T2DM patients is not fully understood (Hong et al., 2013). The most probable explanation can be derived from the damage to the cochlear and retrocochlear structures, such as the vestibulocochlear nerve, due to minor glycaemic variations leading to unstable inner ear function (Çayönü, Çapraz, Acar, Altundağ, & Salihoğlu, 2014; de David et al., 2018; Mahallik, Sahu, & Mishra, 2014). According to de David et al., (2018), the small blood vessels in the auditory system are mostly affected by the physiological changes which supply the integral structures with the necessary chemical balance for proper function. In addition, the inner ear has no energy reserves and these small metabolic changes could lead to decreased oxygenation of the hair cells, spiral ganglion atrophy, eighth nerve myelin sheath degeneration and decreased nerve fibres in the spiral blade (de David et al., 2018).

Along with the complexity of understanding the cause of the degeneration within the auditory system, various assessment methods were used for the identification thereof (Hong et al., 2013). In the past, the assessment was limited to the use of pure tone audiometry. However, a greater need exists for a measure of subclinical hearing changes to identify damage of the 8th cranial nerve before symptoms of hearing loss occur as supported in the conclusions of de David et al., (2018), de León-Morales, Jáuregui-Renaud, Garay-Sevilla, Hernández-Prado, & MalacaraHernández, (2005), Durmus, Yetiser, & Durmus, (2004) and Hong et al., (2013). These subclinical hearing changes or undetected hearing loss could lead to a decrease in the overall quality of life especially with regards to social interaction and communication function (Nakajima, Kanda, Hosobuchi, & Suwa, 2014). However, more research is still needed to fill the void of the sensitivity of these measures used for identification of subclinical hearing loss in patients with T2DM (Durmus et al., 2004; Hong et al., 2013).

1.3. Type 2 Diabetes Mellitus and Auditory Brainstem Response measures

Auditory Brainstem Responses (ABR) is a non-invasive measurement used for the study of the electrical potentials evoked in the auditory neural pathway in response to acoustical stimuli (Siddiqi et al., 2013; Sushil, Muneshwar, & Afroz, 2016). The ABR wave is dominated by several peaks, with wave I, III and V being the most reliably recorded for clinical use. Each of the waves corresponds to a specific neural generator within the auditory neural pathway. Figure 1 shows how the specific wave can be designated to a site in the auditory neural pathway specifically wave I being the distal part of the acoustic nerve, wave III the superior olivary complex and wave V the inferior colliculus (Siddiqi et al., 2013).

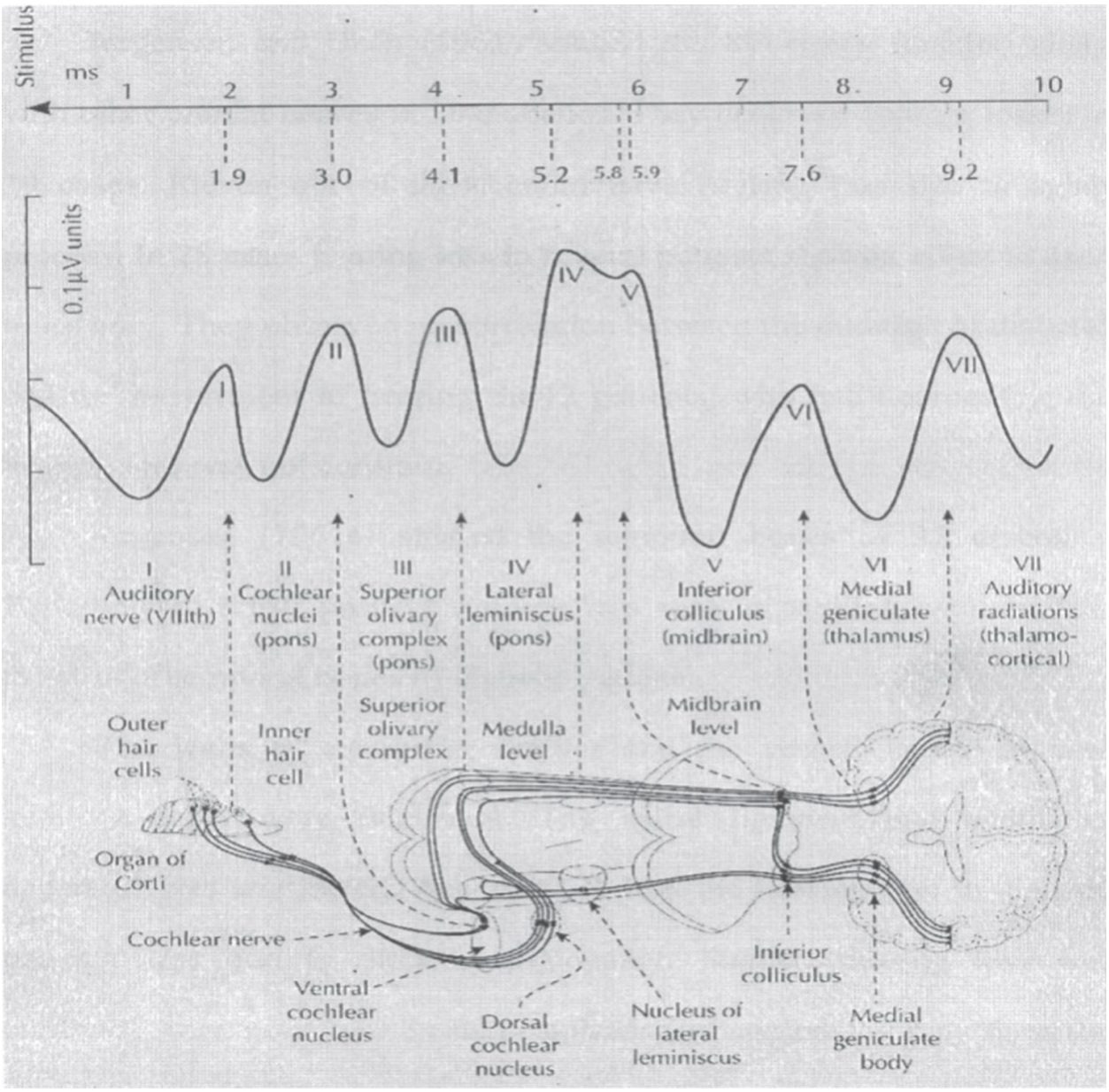

Figure 1: ABR wave morphology and latencies in a normal hearing participant (Siddiqi et al., 2013)

These five ABR peaks are obtained by the use of various stimulus and acquisition parameters, one of which is the stimulation rate (Hall III & Mueller III, 1997; Takkar et al., 2015). The amplitudes of these peaks can vary among the populations however, the latencies of the ABR peaks are stable in normal hearing individuals when using the standard ABR testing protocol, with wave V being the most robust (Hall III, 2007; Hall III & Mueller III, 1997; Siddiqi et al., 2013; Takkar et al., 2015). The interpeak latencies of wave I-III, III-V and I-V give an indication of the auditory neural pathway from the level of the brainstem to the midbrain. Any increase of the absolute and interpeak latencies could

indicate possible changes within the auditory system at the specifically involved neural generators, such as the vestibulocochlear nerve and other brainstem and/or midbrain centers (Ackley, Herzberger-Kimball, Burns, & Balew, 2012; Siddiqi et al., 2013; Takkar et al., 2015).

The significance of ABR's in the subclinical identification of hearing loss with T2DM patients was the focus of a study done by Durmus et al., (2004). The study compared three groups of, normal hearing participants namely; those with Type I Diabetes Mellitus, T2DM and a control group without Diabetes Mellitus. A significant prolongation of ABR absolute latencies of waves I, III and V were identified in the diabetic participants when compared to the control group. However, between the two diabetic groups, only the absolute latencies of waves III and V were significantly more delayed for the T2DM group. The interpeak latencies of waves I-V and III-V between the control group and the diabetic groups were identified to be significantly prolonged (Durmus et al., 2004). These increases of wave latencies for normal hearing diabetic participants led the researchers to conclude that the use of standard protocol ABR results, without any additions such as rate changes, may identify patients with diabetes who are at risk of developing subclinical central hearing impairments. In addition, Durmus et al., (2004) mention a latent period of detectible permanent hearing impairment and the importance of identifying 8th cranial nerve damage with the use of ABR measures. The inclusion of various stimulation rates, and the resulting decreased neural recovery time will lead to greater sensitivity and possible earlier detection of small neurological changes, especially for those with controlled blood glucose levels (Hood, Linda, 1998).

Closely related to this is the study by Mahallik et al., (2014) that supports the presence of ABR absolute and interpeak latency prolongations within the age group of 25 to 45year-old normal hearing adults with T2DM when compared to age-matched healthy participants. Wave I absolute latencies and III-V interpeak latencies in both ears were significantly delayed. The right ear ABR results also indicated a prolongation of wave V absolute latency and all the interpeak latencies. The left ear, however, showed wave III absolute latencies and interpeak latencies of wave's I-III and I-V to be prolonged. As with Durmus et al., (2004), they found that the degeneration in the auditory system seems to be more central than peripheral and that the neural conduction within the participants with T2DM's auditory system slows down before any noticeable hearing implications are reported.

De León-Morales et al., (2005) also identified an increase of the interpeak latencies for III-V and I-V and the absolute wave V latency for 94 diabetic patients when compared to a healthy control group. These patients were within ±50 years of age and included both men and women. However, the T2DM participants did present with mild high frequency hearing losses which differ from those mentioned in Durmus et al., (2004) and Mahallik

et al., (2014) who had hearing levels below 20dB. The group with diabetes in this study had blood glucose levels corresponding to the uncontrolled blood sugar level group of Sushil et al., (2016). Sushil et al., (2016) studied 60 patients with T2DM which were divided into two groups based on whether their blood sugar levels were controlled or uncontrolled. The participants were between the ages of 35 to 50 years and included both genders. Both groups had equal latencies for wave I but a significant delay was observed for wave II and III absolute latencies and the interpeak latencies for wave's I-III in the uncontrolled blood glucose group. As with the diabetic group of the previous study, the uncontrolled group also presented with delays of interpeak latencies for wave's III-V and I-V and the absolute latency of wave V (de León-Morales et al., 2005; Sushil et al., 2016). These prolongations support the risk T2DM patients have for developing later hearing impairments caused by the changes in the auditory neural pathway which specifically relate back to the nerve functioning (Durmus et al., 2004).

Another study focused on 126 T2DM diagnosed adult males and 106 age-matched healthy participants (Gupta et al., 2013). All the participants also had normal peripheral hearing sensitivity. The researchers found that the T2DM group aged 35 to 50 years showed prolongation of absolute ABR latencies of wave III and V and interpeak latencies of III-V and I-V. These prolongations of the ABR latencies in normal hearing adults support changes within the neural functioning of the auditory neural pathway caused by T2DM and match the findings of Durmus et al., (2004) and Mahallik et al., (2014). Ren et al., (2009) had T2DM participants who presented with a mild high frequency hearing loss when tested behaviorally. As with the above-mentioned studies the patients were within the age range of ±40 years and included 50 healthy participants and 50 T2DM participants. As with de León-Morales et al., (2005) and Gupta et al., (2013), a prolongation of the absolute latency for wave V and interpeak I-V latency was observed for patients with T2DM. However, both de León-Morales et al., (2005) and Ren et al., (2009) mentioned the use of two stimulation rates one below 30 Hz (11.1) and the other above at 67.4 Hz and 80.1 Hz respectively for but made no mention as to which of the two was reported on.

Siddiqi et al., (2013) reported an increase of absolute and interpeak latencies for participants 30 years and older. The prolongations were observed at various suprathreshold intensities and there was no perceptual hearing loss mentioned for any of the 25 T2DM or 25 healthy participants. At all the intensities there was a prolongation in the absolute wave III and V latencies and interpeak latencies of I-III, I-V and III-V. Throughout all studies, there was a delay of all absolute and interpeak ABR latencies for T2DM participants. These delays indicate the changes in the neural generators involved with each of these waves and carry a risk for later hearing impairments (Durmus et al., 2004; Ren et al., 2009; Takkar et al., 2015).

1.4. Rationale

The studies discussed above were reported with the use of a standard ABR protocol. For the current study, there was a specific focus on the use of various stimulation rates. Slow stimulation rates used with the standard ABR protocol is used for better wave morphology (Hall III, 2007). Takkar et al., (2015) reported no significant delay in any of the ABR latencies when using a standard, slow stimulation rate. The researchers attributed the lack of latency delay to the good glycaemic control of the participants in the study (Takkar et al., 2015). However, it can be hypothesized that a faster rate could have increased the sensitivity for identifying a possible minor retrocochlear pathology, caused by the T2DM even with good glycaemic control (Ackley et al., 2012; Çayönü et al., 2014; Hall III, 2007; Mahallik et al., 2014). This could be due to the decrease in time the auditory nervous system has for neural recovery thus causing a greater delay in the ABR latencies (Ackley et al., 2012).

The important role ABR measures play in identifying individuals with T2DM who have prolonged ABR latencies with no perceptual hearing loss have been thoroughly discussed. However, the addition of a rate study to the standard ABR protocol may afford greater sensitivity to auditory neurological degeneration, specifically regarding T2DM and its effects on the auditory neural components. An increased stimulation rate leads to decreased neural recovery time, and may result in a delay in wave V latency with the use of faster stimulation rates as the auditory nervous system is already burdened by pathology (Ackley et al., 2012). Zakaria, Wahab, & Awang (2017) also reported that no correction is necessary for older aged participants as commonly found in the T2DM population with the use of a rate study. To date, there are no previous studies that evaluated the effect on increased stimulation rate on adults with T2DM (Ackley et al., 2012). As T2DM is a growing worldwide the importance of including the ABR assessment with rate studies as part of the standard diabetes health monitoring has become of great importance to us as hearing health care professionals. Thus, the aim of the current study was to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates.

CHAPTER 2

METHODOLOGY

CHAPTER 2: METHODOLOGY

2.1. Research aim

The main aim of this study was to assess the auditory neural function of adults with Type 2 Diabetes Mellitus, presenting with normal behavioural audiometric thresholds, by means of Auditory Brainstem Responses with various stimulation rates.

2.2. Research design

The research was descriptive in nature regarding the ABR latencies and the impact of various stimulation rates in T2DM participants when compared to non-diabetic gender and age-matched adults (Babbie & Mouton, 1998). The research process was a cross-sectional study design with within-subject repeated measures (Morris & DeShon, 2002). Numerical information, the ABR wave latencies, was obtained and therefore a quantitative data analysis method was used for this research study.

2.3. Objectives of the study

- Asses auditory neural function of normal hearing adults with standard ABR rate
- Use of rate study to determine sensitivity with regards to identification of subclinical hearing impairments

2.4. Ethical considerations

2.4.1. Permission

Before data collection commenced ethical clearance was applied for from the Research and Ethics Committee at the Department of Speech-Language Pathology and Audiology. Once departmental clearance was obtained, application for ethical approval was completed and granted by both the Research Ethics Committee of the Faculty of Health Sciences (Appendix A) and the Research Ethics Committee of the Faculty of Humanities (Appendix B). The ethical clearance from the above mentioned faculties was made available to the Diabetes Clinic at Steve Biko Academic Hospital (SBAH) (Appendix C, D & E), Dr Frans Erasmus Diabetic Clinic (Appendix F & G) and Drs. Joynt, Venter & van Rensburg and associates at Park Medical Centre (Appendix H & I) and permission from these various clinics and hospitals were granted to carry out the study and also gain access to their patient records when needed. The structure and procedures of the study were in accordance with the Declaration of Helsinki (last updated in October 2013) which guides researchers in biomedical research involving human subjects (Appendix J).

2.4.2. Informed consent

All potential participants, for the experimental and control group, were asked to sign a written informed consent (Appendix K & L) in English before any further participant

selection or experimental procedures were conducted. Any participation in the study was on a voluntary basis and participants were also made aware thereof. Each participant received verbal and written information on what the study entailed and their rights throughout the research process which included their right to withdraw from the study at any time without any negative consequences (Balnaves & Caputi, 2001). Participants were required to be literate and read and understand English, if the participant was not able to understand the researcher, due to language differences, the researcher either changed languages if able to or asked the assistance of a willing staff member to explain the information letter for better clarification of the research study or the participant was not included in the study population. The information was presented in terminology that the participant understood.

2.4.3. Confidentiality and anonymity

Confidentiality of all participants' identity and personal information was assured (Gravetter & Forzano, 2012). Participants were provided with a unique alpha-numeric code (e.g. 001A) to ensure anonymity during the entire research process and for recording data regarding a specific participant (Appendix M & N). The participants' identity was only known by the researcher. All personal information revealed during the testing sessions was kept in the strictest confidence.

2.4.4. Avoidance to do harm

The researcher took all the necessary steps to ensure that none of the participants was exposed to any physical or emotional harm (Gravetter & Forzano, 2012). Careful considerations were taken to ensure that all objective measures and blood glucose assessment were conducted quickly and accurately to ensure the participants were not fatigued or discomforted excessively due to testing procedures. Participants were encouraged to sleep during ABR assessment to decrease myogenic interference and decrease testing time. Those who did not fall asleep were given auditory breaks between each rate to ensure the least amount of auditory discomfort. According to the World Health Organization (WHO) (2014), the maximum amount of time during the day for exposure to 80 dB is 25 hours for safe listening. As the current study set out to assess each participant within 1 and ½ hours the exposure time was still well within the safe listening timeframe.

2.4.5. Honesty

Participants were given access to their own test results (Appendix O) and the results of the study upon completion. The study was submitted to be published as an article in a scientific peer-reviewed journal with acceptance pending (Nov 2018). The results were presented in the form of a master's degree dissertation. Data is being stored electronically on a compact disk (CD) at the University of Pretoria's Department of

Speech-Language Pathology and Audiology (Appendix P). The study was supervised and reviewed by two internal supervisors (Dr Biagio de Jager and Prof. Paul Rheeder).

2.4.6. Plagiarism

The study and written report of the study was the researchers own original work. All secondary material cited was carefully acknowledged and referenced according to APA referencing guidelines. The study adheres to the University of Pretoria policy on plagiarism. A declaration of originality can be found in Appendix Q.

2.4.7. Reliability and Validity

Reliability and validity were ensured by the following features of this research study:

- The use of objective testing procedures for data collection.
- The subjective interpretation of the ABR results was compensated for by the use of two independent professionals who were consulted with regards to the marking of wave point information.
- Testing environments and conditions were the same for all participants.
- The use of the same testing equipment for all participants throughout the study.
- All equipment used for both participant selection and data collection has been calibrated prior to the start of data collection (Latest calibration 22/03/2018).
- The testing procedures were kept the same for all research participants.
- To ensure accuracy, all participants received the same instructions which were easy to understand.

2.4.8. Bias

Tympanometry and reflexes are objective tests which were therefore not influenced by tester or participant bias. The ABR interpretation is subjective and tester bias was compensated by consulting two independent professionals in addition to the researcher. They assisted in the process of marking the ABR wave.

2.4.9. Anticipated Benefits

Taking part in the research study did not benefit the participants directly, but the results obtained assisted the researchers in better determining the auditory neural function of individuals with Type 2 Diabetes Mellitus compared to healthy participants. If any audiological problems were identified in the participants they were provided with the written results and a referral letter for further diagnostic assessments and management should they wish to do so.

2.5. Participants

The current study made use of a non-probability purposive sampling technique in the identified population at a Diabetics Clinic. These participants were diagnosed with T2DM either at the clinic or elsewhere. A power analysis (Appendix R) indicated a minimum sample size of 30 participants in each group which allowed the detection of differences between 1 and ½ standard deviation with 80% power and alpha set at 0.05. It will also detect a difference in proportions of 20% or more. Gender distribution was 60% and 40% for females and males respectively. The diabetic participants were recruited from the Diabetic Clinic at Steve Biko Academic Hospital, Dr Frans Erasmus Diabetic Clinic or Drs. Joynt, Venter & van Rensburg and associates at Park Medical Centre. The data collection took place between February-May 2018.

2.6. Test environment and testing personnel

The tests and procedures were all conducted by the researcher as the primary author of this study. Testing was conducted in a quiet room at the various hospitals or clinics for the T2DM participants and at the Department of Speech-Language Pathology and Audiology for control group participants. There were no concerns regarding noise or electrical artefacts while testing.

2.7. Participant selection criteria

Participant selection procedures (described in 2.7.2) were used to determine if the participants have normal hearing and fit the following selection criteria explained in table 1, table 2 and table 3:

Table 1: Participant selection criteria: Inclusion for experimental group

Inclusion criteria and rationale	
Criteria	**Rationale**
Participants diagnosed with T2DM were included based on the diagnostic criteria of the American Diabetes Association (ADA, 2014).	The criteria for the diagnoses of T2DM according to the ADA, (2014) is as follow: • Fasting Plasma Glucose (FPL) level higher or equal to 126mg/dL (7.0 mmol/L) • Two hour- 200 mg/dL or higher plasma glucose level during an Oral Glucose Tolerance Test (OGTT). • Random plasma glucose level of 200mg/dL (11.1 mmol/L) or higher for patients with symptoms of a hyperglycaemic crisis.
Age range between 20 and 60 years.	The highest risk of T2DM is within this age range of 40-60 years (Cherney, 2016; de David et al., 2018). Most commonly T2DM is diagnosed during this age as many patients do not typically present with hyperglycaemia symptoms when younger; however, with greater awareness of T2DM and better identification some participants might be of younger age.

Normal behavioural hearing thresholds obtained with pure tone audiometry.	Participants were only included if they had a Pure tone average (PTA) better than 25dB HL where a slight hearing loss might be present, but speech understanding was not reportedly affected as determined by subjective opinion of each participant during the interview. This cut-off level together with a three frequency PTA (0.5, 1, 2kHz) was used as a majority of the participants in this study could have a possible age-related hearing loss which affects the high frequencies and could already present with some degree of decreased hearing function (Hlayisi et al., 2018).

Table 2: Participant selection criteria: Inclusion for control group

Inclusion criteria and rationale	
Criteria	**Rationale**
Participants with no T2DM.	To ensure the exclusion of T2DM participants for the control group the participants were asked about their current DM status. Previous testing for DM and their family history of T2DM was also asked. Contour TS Blood glucose monitoring system will be used on the day of testing to test their blood glucose to ensure it falls within the normal limits of 4 mmol/L and 8 mmol/L two hours after eating (Ceriello & Colagiuri, 2008).
Age and gender-matched participants.	For accuracy of comparing the results obtained in the research study, control group participants were age and
	gender-matched within ±2 years from the participants in the experimental group.
Normal behavioural hearing thresholds obtained with pure tone audiometry.	Participants were only included if they had a PTA better than 25dB HL. This cut-off level together with a three frequency PTA (0.5, 1, 2kHz) was used as a majority of the participants in this study could have a possible age-related hearing loss which affects the high frequencies and could already present with some degree of decreased hearing function (Hlayisi et al., 2018).

Table 3: Participant selection criteria: Exclusion for both groups

Exclusion criteria and rationale	
Criteria	**Rationale**
No past/present or family history of hearing pathologies, ear pathologies or deafness other than age-related hearing difficulties.	Participants have an increased risk of clearly defined symptoms of hearing loss that could be caused by specific hearing and ear-related pathologies.

No past/present use of ototoxic medication (specifically those used in the treatments of cancer, human immunodeficiency virus (HIV), Tuberculosis (TB), etc.) overexposure to damaging levels of noise, head trauma and existing or history of neurological conditions.	Participants have an increased risk of clearly defined symptoms of hearing loss that could be caused by environmental influences (Rabinowitz, n.d.). Ototoxic medication (that cause damage to the inner ear tissue and vestibulocochlear nerve neurons) can cause otological side effects such as tinnitus and hearing loss (Bisht & Bist, 2011). Noise exposure along with head trauma and neurological conditions could all increase the possibility of hearing loss which would affect the ABR responses. Thus, to ensure the independent study of T2DM's effect on the auditory system individuals identified with these risks were excluded from the study.
History of chronic smoking or alcohol abuse.	The use of alcohol and/or smoking chronically could have an effect on the hearing abilities of the participant (Popelka et al., 2000). This could decrease their pure tone thresholds leading to a PTA worse than the 25dB HL cut-off which is contradictory to the current study's inclusion criteria.
Outer or middle ear pathology that can be ruled out by the use of: • Normal/clear ear canals and tympanic membranes should be observed by the researcher. • Type A tympanometry with a Y-226 Hz probe tone. Values of middle ear pressure between -100 daPa and +100 daPa, compliance between 0.3 ml and 1.75 ml and ear canal volume of 1.0 - 1.4ml are deemed normal (Jerger, 1970) • Present screening ipsi-lateral stapedial acoustic reflexes measured presented at 80-90dB at 0.5,1,2 and 4 kHz (Katz, Medwetsky, Burkard, & Hood, 2009)	Outer and middle ear pathologies could have an effect on the wave amplitude and latencies of ABR responses (McGee & Clemis, 1982). It is thus important that a participant does not present with middle ear pathology as this could be the reason for the amplitude and latency changes in the healthy participants.

2.8. Participant selection

2.8.1. Equipment for participant selection

The material and equipment used for the selection of the participants with regards to the inclusion and exclusion criteria are described in table 4.

Table 4: Material and equipment for participation selection

Material	**Purpose and description**	**Appendix**
Patient information and informed consent form	This informed the participants of the nature and aim of the study and also their rights throughout the research period. Those who were willing to partake in the study were asked to complete the informed consent form and return it to the researcher.	Appendix K & L
Data capturing sheet	The including and excluding factors and results of each participant were recorded on this form.	Appendix M & N
Equipment	**Purpose and description**	**Calibration**

Contour TS Blood glucose meter	This system is used as a test for blood glucose levels for all participants in this study. The participant will be tested on the day using the Contour TS to ensure that their blood glucose levels were within the normal limits of 4 mmol/L to 8 mmol/L two hours after eating (National Institute for Health and Care Excellence (NICE), 2018).	NA
Welch Allyn pocket otoscope	Otoscopy was done to ensure the external ear canal and tympanic membrane(TM) was clear from any visible pathology that could influence the test results or place the participant in harm's way should probe tips or earphones be placed in the ear.	NA
Interacoustics AT235	Tympanometry with a Y-226 Hz probe tone and screening ipsi-lateral stapedial acoustic reflexes at 0.5, 1, 2 and 4kHz was completed to rule out any middle ear pathology that could influence the results.	Last calibration date: 22/03/2018
	Behavioural pure tone threshold testing was performed as part of the exclusion criteria to determine the participants three frequency PTA.	

2.8.2. Procedure for participant selection

Testing commenced once a participant has been selected for the research study and all the procedures were explained and informed consent was signed. All test procedures took place on the same day and took ±60 to 90 minutes. Once the participant was in compliance with the inclusion criteria and there were no excluding factors further data collection commenced as seen in **2.9 Data collection**.

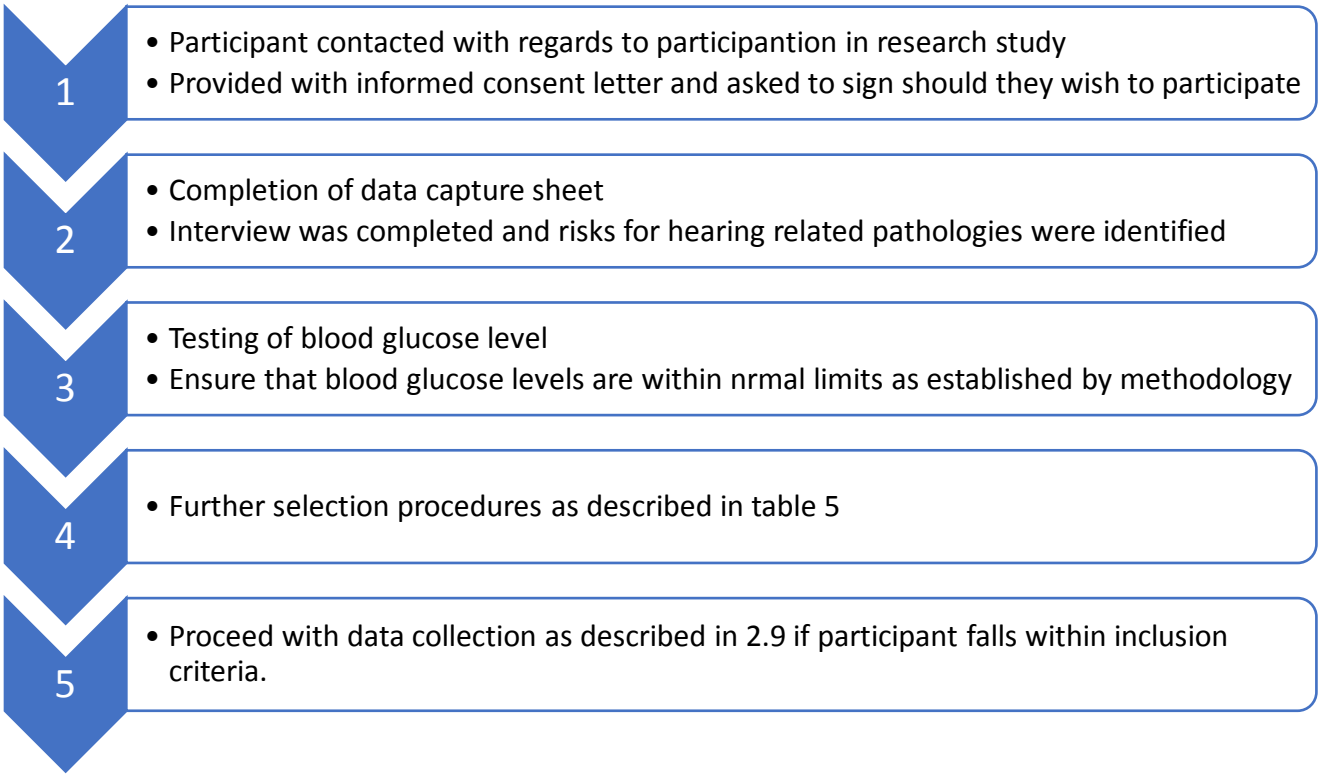

Figure 2: Procedure for participant selection

Table 5 explains the participant selection procedures completed before data collection.

Table 5: Participant selection procedures

Test	Purpose of the test	Instructions to participants	Results deemed normal	Results deemed abnormal
Testing the blood glucose level	This test was completed to ensure that their blood glucose levels were within the normal limits/controlled and rule out possible undiagnosed T2DM in control group participants.	The participant was instructed on why the test will be done then the examiner cleaned the surface area and used the needle pen (a new needle and strip was used for each participant) to draw blood and apply to the testing strip.	The normal limits of 4 mmol/L to 8 mmol/L two hours after eating was used for the control group participants (Ceriello & Colagiuri, 2008)	Any glucose levels below 4 mmol/L or above 8mmol/L
Otoscopy	Otoscopy was done to ensure the external ear canal and TM is clear from any visible pathology that could influence the test results or	The participant was instructed to sit comfortably and still in a chair while the researcher examines their ears.	The researcher should observe the normal structures within the ear canal and on the TM including: • TM that looks healthy	Should the researcher identify any abnormalities such as: • Scarring on the TM

	place the participant in harm's way should		• Light reflex	• Blood or foreign bodies in the ear canal
	probe tips or earphones be placed in the ear.		• Umbo • Clear ear canal (DeRuiter, M., Ramachandran, 2010)	• Infection • Perforation of the TM • Occluding wax (Stach, 2010)
Acoustic Immittance	Tympanometry with a Y-226 Hz probe tone to rule out any middle ear pathology that could have influenced the results.	The participant was instructed to sit comfortably, still and not swallow or talk during the test. They were informed of the slight pressure build up that they will experience once the probe tip has been placed in their ear but that no feedback is needed from them.	Type A tympanometry with a Y-226 Hz probe tone. Values of middle ear pressure between -100 daPa and +100 daPa, compliance between 0.3 ml and 1.75 ml and ear canal volume of 1.0 - 1.4ml are deemed normal (Jerger, 1970)	If any of the values are outside the normal limits the classification will be type As, Ad, B or C tympanograms.
Screening Reflexes	Screening ipsi-lateral stapedial acoustic reflexes at 0.5, 1, 2 and 4kHz to rule out any middle ear pathology that could have influenced the results.	The participant was instructed to sit comfortably, still and not talk during the test. They were informed of the loud sounds that they will hear once the probe tip has been placed in their ear but that no feedback is needed from them.	Present screening ipsi-lateral stapedial acoustic reflexes measured at 0.5,1,2 and 4 kHz (Katz et al., 2009)	If no reflexes are obtained at the frequencies tested
Pure tone audiometry	Behavioural pure tone threshold testing was performed as part of the exclusion criteria to determine the participants PTA.	The participant was instructed to indicate (by raising their hand) when they hear the pure tone sound (beep). They were informed to respond even if the sound is very soft.	The PTA threshold is better than the 25dB HL cut-off (Hlayisi et al., 2018)	If the thresholds obtained are worse than the 25dB HL cut-off the hearing ability will be classified as mild, moderate, severe or profound (Hlayisi et al., 2018; Roeser, 2013).

2.9. Data collection

2.9.1. Equipment for data collection

The material and equipment used for data collection are described in Table 6.

Table 6: Material and equipment for data collection

Material	**Purpose and description**	**Appendix**
Data capturing sheet	The results of each participant's data were recorded on these forms.	Appendix M& N
Equipment	**Purpose and description**	**Calibration**
Interacoustics Eclipse AEP system	Equipment was used to measure the ABR waves at various stimulation rates for each participant.	Latest calibration date: 22/.3/2018 For a specific peSPL (peak equivalent Sound Pressure Level) value, the maximum acoustical level is calibrated to
		match the level of continuous tones used in obtaining the similar dB SPL reading on a sound level meter. Due to a poor correspondence between the acoustical value given in dB SPL and normal HL figures, there is a difference of 35.3dB for Clicks as AEP stimulation durations are very short and the energy delivered is not perceived with the same subjective loudness as the equivalent stimulus would provide. To compensate for the difference a correction is used namely nHL. Calibration was done using an oscilloscope and measured in dB peSPL the clicks were corrected by 35.5dB resulting stimuli reported in dB nHL.
Insert earphones ER-3A	The use of insert earphones aided in the decrease of background noise and comfort of use by the patient (Hall III, 2007).	

2.9.2. Procedure for data collection

Table 7 below indicates the test protocol used for ABR data collection.

Table 7: ABR test protocol for clinical measures

Stimulus Parameters	**Selection**
Transducer	Insert earphones ER-3A
Type	Click
Duration	0.1ms

Polarity	X1 Rarefaction X1 condensation
Rate	A fast, medium and a slow rate was be used 31.1 Hz 45.1 Hz 61.1 Hz for the detection of reduced neural function
Intensity	80dB nHL
Repetitions	Minimum 2
Acquisition Parameters	
Electrodes Non-inverting (active) Inverting (reference) Ground	 Fz M1, M2 Fpz
Filters HP (high pass) LP (low pass) Notch	 30 Hz 3000Hz None
Amplification	100,000
Analysis time	15 ms
Artefact rejection	±40 µV
Residual noise levels	<40 µV
Impedances	<5kΩ
Number of sweeps	2000-4000 (more if high electrical artefacts)

(Ackley et al., 2012; Hall III, 2007; Hall III & Mueller III, 1997)

ABR testing started with the researcher cleaning the surface area of the skin with a medical Nuprep skin prep gel (Weaver & company) and electrodes were laced with a Ten20 conducting paste (Weaver & company) and secured with tape which aided in keeping the impedance below 5kOhm. The inverting electrodes were connected to the Interacoustics EPA preamplifier's input right and left and placed on the right and left mastoid respectively. The non-inverting (active) silver chloride cup electrode was placed on the high forehead and plugged into the preamplifier at Vertex. The ground electrode was placed on the low forehead (Crumley, 2016). The ER-3A earphones were then inserted into both ears. The participant was instructed that there is no need for a response from their side and it is also recommended that the participant closed their eyes and lie still or even sleep during this procedure to reduce participant artefacts. Various rates were used, including 31.1, 45.1 and 61.1 (Ackley et al., 2012). The auditory response was measured and interpreted by the researcher as well as two other independent interpreters.

2.10. Data analysis

Data analysis is defined as the process of answering research questions by understanding all the results and data from the research study (Statistics Canada, 2009). Descriptive statistics, that was used for the current study, is described as a statistical method that includes numerical data such as means and totals to review all the results obtained from the research study (Gravetter & Forzano, 2012; Statistics Canada, 2009). For the current research study, a descriptive analysis was done to calculate the mean, standard deviations, median and interquartile range for the absolute and interpeak latencies and amplitudes of the ABR waves for the various stimulation rates (StataCorp, 2017). Inferential statistics is described as an inference of our data findings to more general conditions such as the entire population (William, 2006).

In order to take this into consideration, groups were compared with linear mixed models evaluating whether random intercepts for pairs or individuals were needed. Residual analysis was done to determine if their distribution was normal and if there were any outliers present. In some instances (viz. rate 31.1Hz wave I and III absolute latencies and wave I amplitude) pairs were not needed as random intercepts and random intercepts were only used for the individuals (as left and right ears were combined).

A repeated measures analysis of rates with latency as the outcome and rate as the repeated measure was also performed. A mixed model with random intercepts of pairs, individuals and ears (measurements were repeated per ear) was used as the participants were paired and both ears were included. The interaction term (diabetic status*rate) was used to determine if a change in latency over rates depends on whether you have diabetes or not. As this was not significant, a model using diabetes status and rate, excluding the interaction term, was then computed.

CHAPTER 3 RESEARCH ARTICLE:

Auditory neural function of normal hearing adults with Type 2 Diabetes

CHAPTER 3: RESEARCH ARTICLE

Auditory neural function of normal hearing adults with Type 2 Diabetes Mellitus

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3.1. Abstract

Background: The prevalence of diabetes mellitus is growing worldwide. Type 2 Diabetes Mellitus (T2DM) can lead to damage to various organs by affecting the intricate nerve and blood vessel systems in the body caused by hyperglycaemia, including the auditory neural pathway.

Purpose: This study aimed to assess the auditory neural function of adults with T2DM by means of Auditory Brainstem Responses (ABR) with various stimulation rates, presenting with normal behavioural audiometric thresholds.

Research Design: Cross-sectional comparative study of ABR latencies and amplitudes and the impact of various stimulation rates in T2DM participants when compared to gender and age-matched controls without diabetes.

Study Sample: Sixty participants, thirty with T2DM and 30 without T2DM were recruited and gave informed consent. The thirty T2DM participants aged 20-60 years were recruited from three clinics including two private and one public tertiary clinic. The control group consisted of thirty healthy age and gender-matched volunteers. Behavioural audiometry was performed to ensure a normal pure tone average (< 25 dB HL).

Data collection and analysis: The Interacoustics Eclipse Auditory Evoked Potentials (AEP) system was used for the ABR measures which were analysed using linear mixed models. Data consisted of latencies and amplitudes of wave I, III and V and interpeak latencies of I-III, III-V and I-V of the 31.1 Hz rate. Wave V latencies and amplitudes for the 45.1 and 61.1 Hz stimulation rates were also measured.

Results: Wave III latency at 31.1 was significantly delayed in those with T2DM compared to the control group ($p<0.05$). Participants with T2DM presented with prolonged wave V latencies at the faster stimulation rates than those without T2DM, but the shift was not statistically different between groups. Diabetes status had no moderating effect of wave V latency at the different stimulation rates.

Conclusion: The results identified that the rate study was not affected by any confounding variables such as diabetes status and glucose level. However, the subclinical neurophysiological pathology, specifically at the level of the brainstem, as demonstrated by the delay in wave III, may be at least part of the reason for complaints relating to bilateral hearing difficulties in noise

Keywords: Diabetes Mellitus, Type 2 Diabetes Mellitus, Auditory Brainstem Response, rate study, Auditory neural

Abbreviations: T2DM – Type 2 Diabetes Mellitus, µV – microvolt, ms – milliseconds, Hz – Hertz, PTA – Pure Tone Average, DM- Diabetes Mellitus, IQR- Inter Quartile Range, SD- Standard deviation

3.2. Introduction

Diabetes Mellitus (DM) is adding to the global burden of disease as the prevalence thereof increases worldwide. This increase of prevalence can be attributed to higher population size, urbanization, age, obesity and lower physical activity in the population (Wild et al.,. 2004; Hlayisi et al.,. 2018). According to the IDF (2017) 425 million people were living with diabetes in 2017 with an estimated increase of up to 629 million by 2045 with 90% of these attributed to Type 2 Diabetes Mellitus (T2DM). In addition to this, the number of South African adults living with DM is estimated to rise from 5.4% to 6.1% in the same time frame with up to 84.8% still undiagnosed (IDF, 2017). These current statistics bring to mind the concerns for hearing healthcare practitioners and the association between DM and hearing loss, with an on-going discussion about the configuration and degree thereof (Hong et al.,. 2013; Karabulut et al.,. 2014; Krishnappa and Naseeruddin, 2014; Calvin and Watley, 2015). The exact cause of the hearing loss and degeneration of the auditory function is unknown (Hong et al.,. 2013). The most probable explanation can be derived from the damage to the cochlear and retrocochlear structures, such as the vestibulocochlear nerve, due to minor glycaemic variations leading to unstable inner ear function (Çayönü et al.,. 2014; Mahallik et al.,. 2014; de David et al.,. 2018).

Along with the complexity of understanding the cause of the degeneration in hearing sensitivity, various assessment methods are used for the identification thereof (Hong et al.,. 2013). In the past, the assessment was limited to the use of pure tone audiometry. However, recently a need exists for a measure of subclinical hearing changes, such as the Auditory Brainstem Response measure (ABR), to identify damage of the CN VIII other central auditory structures (Hong et al.,. 2013; de David et al.,. 2018).

ABR is a non-invasive measurement used for the study of the electrical potentials evoked in the auditory neural pathway in response to acoustical stimuli (Siddiqi et al.,. 2013; Sushil et al.,. 2016). Five peaks, corresponding to specific neural generators within the auditory neural pathway, dominate the
ABR and are stable in normal hearing adults, with wave V being the most robust (Hall III and Mueller III, 1997; Hall III, 2007; Siddiqi et al., 2013; Takkar et al., 2015). An increase of the wave latencies could indicate possible degeneration within the auditory system at the specifically involved neural generators as is found in individuals with T2DM (Siddiqi et al.,. 2013; Takkar et al.,. 2015).

Previous studies have reported delayed absolute and interpeak latencies with the use of a standard ABR protocol in adults with diabetes. Durmus et al., (2004) and Mahallik et al., (2014) found delays in wave I, III and V absolute latencies and the interpeak latencies indicating both peripheral and central auditory neural degeneration. However, the majority of the studies showed delays in only wave III and/or V absolute latencies thus supporting the theory of degeneration of more central auditory neural functioning (Donald et al.,. 1981; de León-Morales et al.,. 2005; Ren et al.,. 2009; Siddiqi et al.,. 2013; Gupta et al.,. 2013; Sushil et al.,. 2016). Takkar et al., (2015) reported no significant delay in any of the ABR latencies when using a standard neurodiagnostic ABR in T2DM adults grouped according to the duration of disease. The researchers attributed the lack of latency delay to the good glycaemic control of all participants in the study regardless of the duration of their disease. Sushil et al., (2016) had similar findings as the T2DM participants with uncontrolled blood glucose levels had significantly delayed absolute and interpeak latencies when compared to T2DM with controlled blood glucose levels. It may, however, be hypothesized that a faster stimulation rate than that used in existing literature, may have increased the sensitivity of the ABR for the identification of minor retrocochlear pathology, caused by the T2DM even with good glycaemic control (Hall III, 2007; Ackley et al.,. 2012; Çayönü et al.,. 2014; Mahallik et al.,. 2014).

It is clear from previous literature that ABR measures can be used in identifying individuals with T2DM who have prolonged latencies even in the absence of a perceptual hearing loss. However, the addition of a rate study to the standard ABR protocol may afford greater sensitivity to auditory neurological degeneration, specifically regarding T2DM and its effects on the auditory neural components. To date, there are no previous studies that evaluated the effect on increased stimulation rate on adults with T2DM (Ackley et al.,. 2012). Thus, the aim of the current study was to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates.

3.3. Material and Methods

3.3.1 Study participants

Institutional ethical clearance was granted prior to commencement of data collection (Health sciences: 43/2018 and Humanities: 14039789-GW20180201HS) with careful consideration of the rights of all participants. Sixty participants were recruited and gave informed consent. The participants were divided into two groups consisting of 30 participants with T2DM (60 ears) with a mean age of 47 years (SD 10.35) who were recruited from three clinics including two private clinics and the Diabetes Clinic at Steve Biko Academic Hospital. The remaining 30 control group participants without diabetes, age and gender-matched with a mean age of 47.27 years (SD 10.06) (two ears duplicated) were recruited from friends, family and acquaintances.

The participants consisted of 18 females (60%) for each of the experimental and control group. The average age of diagnoses for the diabetic participants was 38.7years (SD 7.87) with a mean duration of T2DM for 8.28 years (SD 7.87). Before audiological investigation a clinical interview was completed to rule out any of the following: past/present family history of hearing pathologies including current outer and/or middle ear pathologies and deafness, past/present use of ototoxic medication (specifically those used in the treatments of cancer, HIV, TB, etc.), overexposure to damaging levels of noise, head trauma and existing/history of neurological conditions or history of chronic smoking or alcohol abuse. Adults who presented with any of the aforementioned were excluded from participation. The strip operated blood glucose test was completed with capillary blood from a small prick to the participants finger, to ensure that their blood glucose levels were within the normal limits (between 4 mmol/L and 8 mmol/L two hours after eating (Ceriello & Colagiuri, 2008) to rule out possible undiagnosed T2DM in control group participants (Mcmillin, 1990). The blood glucose for the diabetic participants was higher with a mean of 8.11 mmoI/L (SD 4.22) compared to that of the control group at 5.78 mmoI/L (SD
1.30).

For all participants, otoscopy and immittance measures were completed to rule out outer and middle ear pathologies. Pure tone air conduction audiometry was conducted with the Interacoustics AT235 portable audiometer. The assessment was performed for each ear with supra-aural headphones to identify hearing thresholds between 250 and 4000 Hz. A three-frequency pure tone average (PTA) was calculated (0.5, 1, 2 kHz). Participants were required to present with a PTA of <25 dB HL (Katz et al.,. 2009; Hlayisi et al.,. 2018). The participants in the diabetic group had a mean PTA of 9.66 dB HL (SD 4.326) whereas the control group participants had a slightly higher mean PTA of 11.21 dB HL (SD 5.608). Both groups had slightly higher hearing thresholds at 4kHz when compared to the overall audiogram with the diabetic group with a mean of 14.67 dB HL (SD 13.96) and non-diabetic with a mean of 15.17 dB HL (SD 12.55).

3.3.2 Auditory Brainstem Responses

The Interacoustics Eclipse AEP system, which was calibrated prior to data collection using peSPL (peak equivalent Sound Pressure Level) and nHL (normal hearing level) as specified in ISO 389-6-2007, was used for the ABR measures. The non-inverting (active) silver chloride cup electrode was placed on the high forehead (Fz) with the ground electrode on the low forehead (Fpz) and the inverting (reference) electrodes on the mastoids (M1, M2). Participants were placed in a reclining position, with their eyes closed and ER-3A insert earphones were used to present a click stimulus at an intensity of 80 dB nHL. Three stimulus rates were used (31.1, 45.1 and 61.1 Hz) and one each repeated at least twice (rarefaction and condensation). The

impedances were measured throughout to ensure levels below 5kΩ. Artefact rejection was set at ±40 µV and bypass filters of 30-3000 Hz were used. After averaging the response for a minimum of 2000-4000 sweeps per trace to ensure that residual noise levels were reduced to <40 µV, the latencies and amplitude for a wave I, III and V and interpeak latencies of I-III, III-V and I-V at the slowest rate were measured. Wave V latencies and amplitudes for the 45.1 and 61.1 Hz rates were then also recorded.

3.3.3 Statistical analysis

Descriptive statistics of variables were described including the mean, median, standard deviation and Interquartile ranges (IQR) of the ABR absolute and interpeak latencies and amplitudes (StataCorp, 2017). Individuals were paired, and tests were done on the left and right ears. In order to take this into consideration, groups were compared with linear mixed models evaluating whether random intercepts for pairs or individuals were needed. Residual analysis was done to determine if their distribution was normal and if there were any outliers present. In some instances (viz. rate 31.1Hz wave I and III absolute latencies and wave I amplitude) pairs were not needed as random intercepts and random intercepts were only used for the individuals (as left and right ears were combined).

A repeated measures analysis of rates with latency as the outcome and rate as the repeated measure was also performed. A mixed model with random intercepts of pairs, individuals and ears (measurements were repeated per ear) was used as the participants were paired and both ears were included. The interaction term (diabetic status*rate) was used to determine if a change in latency over rates depends on whether you have diabetes or not. As this was not significant, a model using diabetes status and rate, excluding the interaction term, was then computed.

3.4. Results

3.4.1. Auditory Brainstem Responses

3.4.1.1. Latency

Table 8 presents the descriptive statistics for the absolute and interpeak latencies of all the recorded ABR waves for those with diabetes and without diabetes.

Table 8: **Mean, standard deviation (SD), median, inter quartiles range (IQR) of the absolute and interpeak latencies for waves I, III and V at rate 31.1 Hz and wave V at rates 45.1 and 61.1 Hz for participants with Type 2 Diabetes Mellitus and controls (n=60)**

Component	Diabetic patients		Non-diabetics patients	
	Mean (SD) (ms)	Median (IQR) (ms)	Mean (SD) (ms)	Median (IQR) (ms)
Wave I_1	1.60 (0.22)	1.57 (1.43;1.76)	1.52 (0.12)	1.53 (1.43;1.60)

Wave III_1	3.85 (0.28)	3.80 (3.64;4.03)	3.68 (0.52)	3.70 (3.61;3.89)
Wave V_1	5.73 (0.43)	5.65 (5.35;6.09)	5.67 (0.31)	5.65 (5.48;5.80)
Wave V_2	5.94 (0.44)	5.90 (5.67;6.28)	5.86 (0.34)	5.77 (5.63;5.99)
Wave V_3	6.12 (0.48)	6.07 (5.77;6.42)	5.96 (0.76)	6.00 (5.80;6.20)
Interpeak $I\text{-}III_1$	2.25 (0.27)	2.25 (2.08;2.49)	2.22 (0.24)	2.20 (2.00;2.33)
Interpeak $III\text{-}V_1$	1.91 (0.24)	1.83 (1.73;2.10)	1.93 (0.28)	1.90 (1.78;2.00)
Interpeak $I\text{-}V_1$	4.15 (0.43)	4.12 (3.83;4.52)	4.15 (0.35)	4.13 (3.90;4.30)

1= Rate 31.1 Hz, 2= Rate 45.1, 3=Rate 61.1

The results for the two-group comparison is given in Table 9. Residual analysis for data using

31.1 Hz rate identified two outliers at wave I and V absolute latencies for each wave respectively; three outliers for waves I-III interpeak latency; and one outlier for the interpeak latency of III-V. One outlier for wave V latency was removed from data using rates 45.1 and

61.1 Hz each. All outliers were excluded from the analysis.

Table 9: Mean difference between participants with diabetes vs participants without diabetes, with 95% Confidence interval (CI) for absolute and interpeak latencies (n=60)

Component	Mean difference (95% CI)	*p*-value
Wave I_1	0.05 (-0.00 - 0.11)	0.079
Wave III_1	0.17 (0.01 - 0.32)	0.027*
Wave V_1	0.07 (-0.05 – 0.23)	0.234
Wave V_2	0.07 (-0.07 – 0.22)	0.341
Wave V_3	0.08 (-0.0 8 – 0.24)	0.322
Interpeak $I\text{-}III_1$	0.05 (-0.02 – 0.12)	0.164
Interpeak $III\text{-}V_1$	0.00 (-0.07 – 0.08)	0.933
Interpeak $I\text{-}V_1$	0.00 (0.12 – 0.12)	0.983

*n=total number of participants; *Statistically significant ($p < 0.05$); 1= Rate 31.1 Hz; 2= Rate 45.1; 3=Rate 61.1*

A statistically significant difference was measured in wave III latency between the participant groups measured at a rate of 31.1 Hz (p=0.027). No statistically significant differences were

found in the absolute and interpeak latencies of waves I, V, I-V, I-III and III-V at 31.1 Hz or at wave V when using rates of 45.1 and 61.1 Hz ($p>0.05$).

3.4.1.2. Amplitudes

The descriptive statistics for the amplitudes recorded for both groups can be seen in Table 10.

Table 10: **Mean, standard deviation (SD), median, inter quartiles range (IQR) of the amplitudes of Wave I, III and V for rates 31.1, and wave V for 45.1 and 61.1 Hz for participants with Type 2 Diabetes Mellitus and controls (n=60)**

Component	Diabetic patients		Non-diabetics patients	
	Mean (SD) (µV)	Median (IQR) (µV)	Mean (SD) (µV)	Median (IQR) (µV)
Wave I_1	0.10 (0.07)	0.08 (0.05;0.13)	0.12 (0.07)	0.10 (0.07;0.16)
Wave III_1	0.20 (0.11)	0.18 (0.11;0.29)	0.20 (0.12)	0.18 (0.11;0.26)
Wave V_1	0.33 (0.16)	0.31 (0.20;0.43)	0.32 (0.12)	0.30 (0.23;0.36)
Wave V_2	0.31 (0.17)	0.27 (0.18;0.39)	0.30 (0.11)	0.30 (0.23;0.36)
Wave V_3	0.28 (0.15)	0.27 (0.16;0.37)	0.24 (0.10)	0.25 (0.17;0.29)

1= Rate 31.1 Hz, 2= Rate 45.1, 3=Rate 61.1

Results regarding the differences between the groups are shown in Table 11. Residual analysis identified one outlier at wave V amplitude rate 31.1 Hz and this was excluded from the analysis before comparing the two groups.

Table 11: **Mean difference between participants with diabetes vs participants without diabetes, with 95% Confidence interval (CI) for amplitudes (n=60)**

Component	Mean difference (95% CI)	*p*-value
Wave I_1	-0.02 (-0.04 – 0.00)	0.119
Wave III_1	0.00 (-0.03 - 0.03)	0.829
Wave V_1	0.00 (-0.04 – 0.05)	0.786
Wave V_2	0.01 (-0.04 – 0.06)	0.709
Wave V_3	0.03 (-0.01 – 0.09)	0.167

*n=total number of participants; *Statistically significant ($p < 0.05$); 1= Rate 31.1 Hz; 2= Rate 45.1; 3=Rate 61.1*

No statistical significance was found between the amplitudes of the diabetic and non-diabetic groups at any of the waves at rates 31.1, 45.1 or 61.1 Hz ($p>0.05$).

3.4.1.3. Rate study

We investigated the effect of diabetes status and glucose level in latency at the various rates. Table 12 displays the linear mixed model regression analysis of DM, glucose, and when both glucose and DM were combined. Residual analysis identified two outliers at rate 31.1 Hz and one outlier at 45.1 and 61.1 Hz each and was excluded from the analysis.

Table 12: Linear mixed model regression analysis: Diabetes Mellitus (DM) vs non-diabetes mellitus, glucose, glucose and DM for wave V latency at rates 31.1, 45.1 and 61.1 Hz

Interaction	Rate 31.1 Hz		Rate 45.1 Hz		Rate 61.1 Hz	
	Co-efficient (95% CI)	*p*-value	Co-efficient (95% CI)	*p*-value	Co-efficient (95% CI)	*p*-value
DM status	0.08 (-0.06 - 0.22)	0.234	0.06 (-0.08 - 0.20)	0.389	0.08 (-0.08 – 0.24)	0.322
DM adjusted for glucose	0.03 (-0.11 - 0.17)	0.619	0.01 (-0.13 - 0.15)	0.899	0.03 (-0.15 – 0.21)	0.722
Glucose	0.02 (0.00 - 0.04)	0.064	0.02 (0.00 - 0.04)	0.063	0.02 (0.00 - 0.04)	0.09
Glucose adjusted for DM	0.02 (0.00 -0.04)	0.113	0.02 (0.00 - 0.04)	0.1	0.02 (0.00 - 0.04)	0.156

**Statistically significant ($p < 0.05$); CI- Confidence interval*

The interaction between DM and glucose was assessed and was found not to be statistically significant for any of the wave V latencies at rats 31.1 Hz (p=0.323), 45.1 Hz (p=0.200) and 61.1 Hz (p=0.865).

The coefficient of glucose indicates the change of wave V latency at the various rates for every 1 mmo1/L increase in glucose levels. However, this increase was not statistically significant at any of the rates. When adjusting for diabetes status glucose no statistically significant effect on the wave V latencies for any of the rates was measured.

Diabetes status alone and after adjusting for glucose levels had no significant effect on the mean differences of the wave V latency at any of the rates.

To answer the question of how wave V latency changes with varying rates between those with DM and without DM a mixed model regression analysis was performed. The initial model included the interaction term (diabetes status*rate) to determine if a change in latency with faster rates is dependant on the participant having DM or not. This was not significant (p=0.97) and the model was repeated excluding the interaction term (diabetes status*rate). Diabetes status was not significant and excluding it from the model did not change the coefficients of the rates which means DM is not a confounder in the relationship between rate and latency. Both models indicated wave V latency mean shifts at rate 31.1 Hz by 0.07 ms (p=0.347) in the participants with DM when compared to those without diabetes but is not statistically significant. At a rate of 45.1 Hz wave V latency increased by a mean of 0.19 ms, and by a mean of 0.37 ms when using a rate of 61.1 Hz from that measured using rate of 31.1 Hz. The increase in wave V latency measured using pairwise comparisons with Bonferroni corrections from 31.1 Hz to the faster rates was highly significant (p<0.001). Table 13 below depicts the differences in latencies at the various rates adjusted for diabetes status.

Table 13: Mean difference, 95% Confidence Interval (CI) and statistical significance within participants with Type 2 Diabetes Mellitus

Rate	Mean difference (95% CI)	*p*-value
45.1 vs 31.1 Hz	0.19 (0.15 – 0.23)	0.001**
61.1 vs 31.1 Hz	0.38 (0.34 – 0.42)	0.001**
61.1 vs 45.1 Hz	0.19 (0.15 – 0.23)	0.001**

***Highly statistically significant (p < 0.001)*

3.5. Discussion

The current study set out to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates. The neurodiagnostic ABR at a rate of 31.1 Hz indicated a statistically significant delay in wave III latency for participants with T2DM compared to participants without T2DM. The mean interpeak latencies of I-III, III-V and I-V at a rate of 31.1Hz for the T2DM group were equivalent to that of the control group as were the absolute latencies and amplitudes of waves I and V.

The significantly delayed wave III latency in adults with T2DM compared to adults without T2DM correlates with previous literature (Donald et al.,. 1981; Durmus et al.,. 2004; Gupta et

al.,. 2013; Siddiqi et al.,. 2013; Mahallik et al.,. 2014; Sushil et al.,. 2016). This indicates central neural involvement up to the superior olivary complex (SOC) (Siddiqi et al.,. 2013). The main contribution of the SOC is for processing binaural input, localizing auditory input and hearing in the presence of background noise (Bellis, 2003). Physiological changes that could lead to functional and structural damages in the auditory system include, microangiopathy or small vascular disease, glycaemic variations due to insulin resistance increases the presence of microvascular and neural damage in the glucose-dependent neural structures, and oxidative stress (Hong et al.,. 2013; de David et al.,. 2018). Studies suggest that the decrease in auditory neural function in T2DM is likely due to a combination of a number of these physiological changes (Durmus et al.,. 2004; Gupta et al.,. 2013; Hong et al.,. 2013).

In contrast to the majority of existing literature, de León-Morales et al., (2005) and Ren et al., (2009) found delays in the absolute latency of only wave V in adults with T2DM, which resulted in delayed interpeak latencies of wave I-V and III-V compared to adults without T2DM. However, the delay in wave V latency reported may possibly be attributed to the degree of hearing loss, rather than by T2DM, as both studies included participants with high frequency hearing loss, although the degree of loss was not specified in either study. A high frequency hearing loss is known to cause a delay in the latency of a click-evoked ABR wave V (Vonk & Beynon, 2018). Both studies also used a slower and fast stimulation rate; the slower rate was 11.1 Hz, and the faster rate 67.4 Hz and 80.1 Hz respectively for de León-Morales et al., (2005) and Ren et al., (2009), but neither made a distinction between the two when reporting on the ABR latencies. The addition of latency data at faster stimulation rates may further have contributed to the delay found in wave V latency, rather than being a consequence of T2DM.

According to Robinson and Rudge (1977) and Ackley et al., (2012) the use of a rapid stimulus rate, with the standard neurological ABR measure, increases the diagnostic sensitivity of the ABR to subtle neurological lesions as it stresses the auditory nervous system burdened with pathology. A significant difference in the latency of wave V was measured with increased stimulation rates in the current study. The mean wave V latencies at each stimulation rate still fell within the expected range, namely below 6.25 ms, as proposed by Ackley et al.,. (2012). The current study measured prolonged mean wave V latencies at the faster rates of 45.1 and 61.1 Hz for the participant group with T2DM than those without T2DM but the shift was not statistically different between groups. This implies that as the stimulation rate increased, the neural recovery time decreased, causing a greater delay in the ABR latencies for adults with T2DM than in adults without T2DM (Ackley et al.,. 2012). This delay is not specific to T2DM and more research is needed with regards to the sensitivity of rate studies specific to T2DM participants.

The current study found that diabetes status was not a confounder in the relationship between rate and latency. In contrast, both Takkar et al.,. (2015) and Sushil et al.,. (2016) concluded that

the good glycemic control demonstrated by their participants with T2DM was the reason for the normal absolute and interpeak ABR latencies described. In addition, Sushil et al., (2016) reported significant wave III delays, and I-III, III-V and I-V interpeak prolongation in adults with poor compared to well-controlled blood glucose levels. The current study differed from the conclusion drawn in these studies as glucose was found not to moderate the wave V latency during the rate study for either participant group. However, the current study did not distinguish between good and poor glycaemic control amongst the participants with T2DM. Further exploration of the use of the ABR rate study, as a more sensitive measure of auditory neural function than that of the neurodiagnostic ABR, in adults with T2DM with poorly controlled blood glucose levels may provide additional insights into the pathophysiology.

The delay in wave III latency and the greater wave V latency shift measured during the rate study in adults with T2DM is nevertheless of clinical value. Clinicians are likely to attribute the source of complaints of binaural hearing, specifically for speech-in-noise, to the high frequency hearing loss often found in adults with T2DM, rather than consider the possibility of subclinical neurophysiological pathology, specifically at the level of the brainstem, as was identified in the current study (Bellis, 2003; Hong et al.,. 2013; de David et al.,. 2018). The combination of peripheral mild hearing loss and brainstem pathology is consequently liable to negatively impact habilitation outcomes in individuals with T2DM (Beck & Bellis, 2007).

3.6. Conclusion

The current study set out to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates. The neurodiagnostic ABR at a rate of 31.1 Hz indicated a statistically significant delay in wave III latency in adults when compared to those without T2DM. The rate study was able to identify more subclinical changes in the auditory neural pathway of participants with T2DM by the prolonged latencies of wave V for the T2DM group but the latencies were not statistically different from the participants without T2DM. Diabetes status was not a confounder in the relationship between ABR rate and wave V latency. The delayed wave III latency and the greater wave V latency shift measured is nevertheless of clinical value. Subclinical neurophysiological pathology, specifically at the level of the brainstem, may, therefore, add to the source of complaints relating to binaural hearing difficulties in noise, in addition to high frequency hearing loss commonly found in adults with T2DM.

CHAPTER 4 CLINICAL IMPLICATIONS AND CONCLUSION

CHAPTER 4: CLINICAL IMPLICATIONS AND CONCLUSION

4.1 Overview

Hearing loss, more specifically in the high frequencies, are associated with Type 2 Diabetes Mellitus (T2DM) (Hong et al., 2013). Auditory brainstem response measures (ABR) play an important role in identifying individuals with T2DM who have subclinical neurological degeneration even in the absence of hearing loss assessed with behavioural audiometry. However, it can be hypothesized that a faster rate could increase the sensitivity for identifying a possible minor retrocochlear pathology, caused by the T2DM. This could be assigned to the decrease in time the auditory nervous system has for neural recovery thus causing a greater delay in the ABR latencies (Ackley et al., 2012). To date, there are no previous studies that evaluated the effect on increased stimulation rate on adults with T2DM (Ackley et al., 2012). Thus, the aim of the current study was to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates.

4.2. Summary of results

The current study set out to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates. The neurodiagnostic ABR at a rate of 31.1 Hz indicated a statistically significant delay in wave III latency for participants with T2DM compared to participants without T2DM. The mean interpeak latencies of I-III, III-V and I-V at a rate of 31.1Hz for the T2DM group were equivalent to that of the control group as were the absolute latencies and amplitudes of waves I and V.

A significant difference in the latency of wave V was measured with increased stimulation rates, the mean wave V latencies at each stimulation rate still fell within the expected range, namely below 6.25 ms, as proposed by Ackley et al.,. (2012). The current study measured prolonged mean wave V latencies at the faster rates of 45.1 and 61.1 Hz for the participant group with T2DM than those without T2DM, but the shift was not statistically different between groups. This implies that as the stimulation rate increased, the neural recovery time decreased, causing a greater delay in the ABR latencies for adults with T2DM (Ackley et al.,. 2012).

4.3. Clinical implications

The literature established a clear link between T2DM and peripheral hearing loss (de David et al., 2018; Hong et al., 2013). Yet even with adults who present with a normal pure tone average (PTA) on behavioural audiometry, the current study identified

demonstrated deficits in the ABR and rate study by the delayed wave III latency, a greater wave V latency shift measured during the rate study in adults with T2DM. The auditory neural degeneration identified implies that the adults with T2DM may present complaints of binaural hearing, specifically for speech-in-noise, due to the high frequency hearing loss often found in adults with T2DM. Clinicians may dismiss this in light of the normal pure tone audiometry, or may attribute this to mildly raised thresholds in the high frequencies, rather than consider the possibility of subclinical neurophysiological pathology, specifically at the level of the brainstem, as was identified in the current study (Bellis, 2003; Hong et al.,. 2013; de David et al.,. 2018).

The combination of mild peripheral hearing loss and brainstem pathology is consequently liable to negatively impact habilitation outcomes in individuals with T2DM, specifically relating to hearing aid fitting. These poorer outcomes are related to the fact that hearing aids, even though making sound audible and improving the signal to noise ratio in the presence of mild peripheral hearing loss, will fail to compensate for the central processing deficits. In addition, aural rehabilitation therapy in conjunction with the use of hearing aid technology should be highly individualized as each person with T2DM will have varied effects of the disease and thus the various degree of difficulties (Beck & Bellis, 2007).

4.4. Critical evaluation

4.4.1. Strengths of the study

- Individual assessment of ABR of a well-characterized adult population of 30 T2DM participants and 30 control group participants (with no history of T2DM) was included in the research study.
- The design of the research study minimised possible confounding influences by controlling age and gender with the matching of the experimental (with T2DM group) and control group (without T2DM group).
- The current study considered the influences smoking could have on the hearing abilities of participants in both those with diabetes and without. Thus, any participants with a history of chronic and heavy cigarette smoking habits were excluded from the study as smoking could decrease the hearing abilities of participants and changes in ABR wave latencies and could influence the independent study of T2DM on the auditory system (Popelka et al., 2000).
- It has been widely researched that both the illness itself and the medications used in the treatment of some chronic illnesses can have detrimental effects on the auditory system. The chronic illnesses such as HIV and TB and ototoxic medications used therefore can cause damage to the inner ear tissue and vestibulocochlear nerve neurons and have otological side effects such as tinnitus and hearing loss (Bisht & Bist, 2011). Thus, to ensure the independent study of

T2DM's effect on the auditory system individuals identified with these conditions were excluded from the study.

- The research study excluded participants with possible peripheral hearing loss by assessing hearing thresholds and middle ear functioning (by use of immittance measures) to ensure the delay in ABR wave latencies were not due to elevated hearing thresholds but the effect of T2DM.
- Individuals identified with possible middle ear pathology and/or hearing loss was referred for further management.
- Auditory brainstem response measures were conducted while participants were in a relaxed state and sleeping was encouraged thus minimizing the influence of participant artefacts on the ABR measures.
- The validity of the ABR marked waves and reported data was increased by asking two objective experienced audiologists to mark the waves.
- The study made use of mixed and linear models of regression to analyse influence on the wave V latency at various stimulation rates for DM alone, glucose alone, the effect of DM when adjusted for glucose, the effect of glucose when adjusted for DM and the interaction between DM and the increase of stimulation rates (DM status*rate). To the researcher's knowledge, no other research has conducted the regression model analysis in ABR measures with various stimulation rates in participants with T2DM.
- To the researcher's knowledge, no previous literature reported on the use of a rate study for the identification of neural degeneration in T2DM participants.

4.4.2. Limitations of the study

- A possible limitation of the study was a small sample size, however, within the time frame of which the study was carried out this was the maximum number of participants that fulfilled the inclusion criteria.
- The current study found that most of the participants in diabetes and age-matched control group population were older, as is typical of the population with T2DM. Some participants may have presented with a minimal high frequency hearing loss at 4000 Hz or greater, despite a pure tone average of <25 dB HL, that could influence the latency of ABR waves when using a click stimulus. However Hood (1998) suggested that an increase in wave V latency would only
  be measured in adults with thresholds of hearing greater than 50 dB HL at 4000Hz. All participants presented with thresholds less than 40 dB at 4000Hz.
- Also, the current study was limited in terms of the time and finances available for each participant thus no in-depth testing, other than the Contour TS finger prick blood glucose meter could be performed to ensure control group participants did not include adults with undiagnosed T2DM. Additionally, some of the participants

with T2DM may have had poorly controlled blood glucose levels due to the duration of disease, not using medication regularly or an unhealthy lifestyle or just usual variation of blood glucose values which may have influenced the ABR measures on the day of testing.

- Although age and gender matching reduced variables in the groups being compared, this clustering of variables limits the type of analysis that can be performed. A single less clustered participant group may have provided further insights into the pathophysiology.
- The current research study did not make any distinction between the duration of the disease amongst those with T2DM.
- The current study did not distinguish between good and poor glycaemic control amongst the participants with T2DM. Further exploration of the use of the ABR rate study, as a more sensitive measure of auditory neural function than that of the neurodiagnostic ABR, in adults with T2DM with poorly controlled blood glucose levels may provide additional insights into the pathophysiology.

4.5. Recommendation for future research

- The current study was performed in a very limited time frame and the participants had to be tested with no additional costs to them, thus the use of blood glucose measures such as the HbA1c in future research may be better able to identify control group participants who might be unaware that they have T2DM.
- A stricter PTA may be used to confirm the findings of the current study as hearing impairments in older participants, specifically in the high frequencies, may influence the latency of click-evoked ABR waves used for testing across the participant groups. For future, the use of a four frequency PTA and/or lower cut-off level for normal hearing (e.g. <15 dB HL) will limit the influence of hearing loss on the ABR measures and ensure the results were purely because of the effect diabetes has on the 8th cranial nerve and not any other hearing-related pathologies.
- The duration of the disease should be considered in future research as this could influence the degree of neural degeneration that has occurred causing either an increase or decrease in ABR wave latencies depending on the prolonged or shorter duration of disease and uncontrolled blood glucose levels.
- Behavioural measures that target the function of Superior Olivary Complex should be further researched to assess the clinical use thereof for identification of auditory neural degeneration and auditory rehabilitation for those diagnosed with T2DM.
- The inclusion of the interaural wave V differences and wave V/I amplitude ratio between that of the T2DM and control group participants

4.6 Conclusion

The current study set out to assess the auditory neural function of adults with T2DM and normal behavioural audiometric thresholds, by means of ABR's with various stimulation rates. The neurodiagnostic ABR at a rate of 31.1 Hz indicated a statistically significant delay in wave III latency in adults with compared to those without T2DM. The rate study was able to identify more subclinical changes in the auditory neural pathway of participants with T2DM by the greater shift in the latencies of wave V at the faster stimulation rates for the T2DM group, although the latencies were not statistically different from those participants without T2DM. Diabetes status alone and after adjusting for glucose level and the glucose level alone and adjusted for diabetes status was found not to be statistically significant for any of the wave V latencies at the various rates thus having no effect on the rate study. Diabetes status was found not to be a confounder in the relationship between ABR rate and wave V latency. The delayed wave III latency and the greater wave V latency shift measured is nevertheless of clinical value. Subclinical neurophysiological pathology, specifically at the level of the brainstem, may, therefore, add to the source of complaints relating to binaural hearing difficulties in noise, in addition to high frequency hearing loss commonly found in adults with T2DM.

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Appendices

Appendix A:

Letter of clearance from the Research Ethics Committee of the Faculty of Health Sciences

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

1/02/2018

Approval Certificate
New Application

Ethics Reference No: 43/2018

Title: Auditory neural function of normal hearing adults with Type 2 Diabetes Mellitus

Dear Lucresia Kruger

The **New Application** as supported by documents specified in your cover letter dated 18/01/2018 for your research received on the 23/01/2018, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 31/01/2018.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**43/2018**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

☎ 012 356 3084 ✉ deopeka.bahan@up.ac.za / fhsethics@up.ac.za 🖱 http://www.up.ac.za/healthethics
Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60 / 61, 31 Bophelo Road, Gezina, Pretoria

Appendix B:

Letter of clearance from the Research Ethics Committee of the Faculty of Humanities

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

5 March 2018

Dear Ms Kruger

Project:	**Auditory neural function of normal hearing adults with type 2 diabetes mellitus**
Researcher:	**L Kruger**
Supervisors:	**Prof B Vinck and Dr L Biagio de Jager**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**14039789 (GW20180201HS)**

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 1 March 2018. 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 the 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 Studies and Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail:tracey.andrew@up.ac.za

cc: Prof J van der Linder (Acting-HoD)
Prof B Vinck (Supervisor)
Dr L Biagio de Jager (Co-supervisor)

Appendix C:

Permission letter to the CEO of Steve Biko Academic Hospital (SBAH)

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Steve Biko Academic Hospital

January 2018

Dr Ernest Kenoshi

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Chief Executive Officer
Steve Biko Academic Hospital
Private Bag x169
Pretoria
0001

Dear Dr Ernest Kenoshi

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Lucresia Kruger (Student number: 14039789) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetic Clinic at Steve Biko Academic Hospital with Prof Paul Rheeder and Dr Tanja Kemp. If permission is granted, I plan to start with data collection from January 2018.

The title of my study is: **AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS**

This study will aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. The results of the current study can assist researchers in better determining subclinical hearing loss in individuals with Type 2 Diabetes Mellitus compared to healthy participants. If any audiological problems

are identified in the participants I will provide them with the results and a referral letter to the Department of Speech-Language Pathology and Audiology at the University of Pretoria for further investigation should they wish to do so.

Please find attached the Access to Information form as I will be obtaining information from the patient's files.

Thank you for considering this request.

If you require any further information, contact:
Lucresia Kruger (student researcher)
at lucresiak@gmail.com or 084 626 6585.

Sincerely,

Lucresia Kruger
Student Researcher

Dr Leigh Blaglo de Jager
Research Supervisor
Email: leigh.blaglo@up.ac.za

Prof Bart Vinck
Research Co-supervisor
Email: bart.vinck@up.ac.za

I, Dr Ernest Kenoshi, ereby give written permission for the researchers to conduct this research study at Steve Biko Academic Hospital.

Dr Ernest Kenoshi
The Chief Executive Officer at Steve Biko Academic Hospital

Appendix D:

Permission letter to the Head of the Diabetes Clinic- Prof Paul Rheeder at Steve Biko Academic Hospital (SBAH)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE HOSPITAL

Steve Biko Academic Hospital – Diabetes Clinic

January 2018

The Diabetes Clinic
Steve Biko Academic Hospital
Pretoria

Dear Prof Paul Rheeder,

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Lucresia Kruger (Student number: 14039789) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Diabetic Clinic at Steve Biko Academic Hospital. If permission is granted, I plan to start with data collection from January 2018.

The title of my study is: **AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS**

This study will aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. The 30 participants in my experimental group will undergo a single assessment lasting a minimum of 1-1 ½ hours at the Diabetic Clinic of Steve Biko Academic Hospital. The participants will undergo blood glucose testing, auditory tests (otoscopy, acoustic immittance measurements and pure tone audiometry) and an Auditory Brainstem Response assessment.

Faculty of Humanities
Department of Speech-Language Pathology and Audiology
Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

Thank you for considering this request.

If you require any further information, contact:
Lucresia Kruger (student researcher)
at lucresiak@gmail.com or 084 626 8585.

Sincerely,

Lucresia Kruger
Student Researcher

Dr Leigh Blaglo de Jager
Research Supervisor
Email: leigh.blaglo@up.ac.za

Prof Bart Vinck
Research Co-supervisor
Email: bart.vinck@up.ac.za

I, Prof Pau Rheeder, hereby give written permission for the researchers to conduct this research study at the Diabetic Clinic of Steve Biko Academic Hospital.

Prof Paul Rheeder
Head of the Diabetic Clinic of Steve Biko Academic Hospital
Email: paul.rheeder@up.ac.za

Faculty of Humanities
Department of Speech-Language Pathology and Audiology
Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go lwa

Appendix E:

Permission letter to the CEO of Steve Biko Academic Hospital (SBAH) for access to patient files and records

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Permission to access Records / Files / Data base at SBA Hospital

TO:
The (CEO) Chief Executive Officer of SBA Hospital

Re: Permission to do research at SBA Hospital

TITLE OF STUDY: Auditory neural function of normal hearing adults with type 2 DM

This study is approved by the relevant Head of Department (HOD): Prof G Fritzinger Signature: [signature]

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000

I am a researcher / student at the Department of Audiology at the University of Pretoria / _____ Hospital. I am working with Prof P Kheede. I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. This study involves clinical research.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Print Name P. Kheede Signature [signature] on behalf of Lucretia Kruger.
Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved, on condition that there will be no cost to the hospital.

Title and name of Chief Executive Officer: Dr TT Mavundla

Name of hospital / clinic: Steve Biko Academic Hospital

Signature: [signature] Date: 2018/01/10

GAUTENG PROVINCIAL GOVERNMENT
DEPT VAN GESONDHEID
STEVE BIKO AKADEMIESE HOSPITAAL
STEVE BIKO ACADEMIC HOSPITAL
2018 -01- 10
PRIVAATSAK/PRIVATE BAG X169
PRETORIA 0001
GAUTENG PROVINCIAL GOVERNMENT
DEPT OF HEALTH

Appendix F:

Permission letter to Dr Frans Erasmus Diabetes Clinic

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE CLINIC

Dr Frans Erasmus- Diabetes Clinic

February 2018

Dr Frans Erasmus
Diabetes Clinic
29 Jan Booysen Street
Annlin
Pretoria
0182

Dear Dr Frans Erasmus

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Lucresia Kruger (Student number: 14039789) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Dr Frans Erasmus Diabetes clinic.
If permission is granted, I plant to start with collection from February 2018.

The title of my study is: **AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS**

This study will aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. The results of the current study can assist researchers in better determining subtle auditory neurological changes in individuals with Type 2 Diabetes Mellitus compared to healthy participants. If any audiological problems are identified in the participants I will provide them with the results and a referral letter to the Department of Speech-Language Pathology and Audiology at the University of Pretoria or any other private Audiologist for further investigation should they wish to do so.

Thank you for considering this request.

If you require any further information, contact:
Lucresia Kruger (student researcher)
at lucresiak@gmail.com or 084 626 8585.

Sincerely,

Lucresia Kruger
Student Researcher

Dr Leigh Biagio de Jager
Student Researcher

I, Dr Frans Erasmus hereby give written permission for the researchers to conduct this research study at Steve Biko Academic Hospital.

Dr Frans Erasmus
The Chief Executive Officer at

DR. F.F. ERASMUS
PR. No. 149 2373
29 JAN BOOYSEN ST.
ANNLIN
0129

DR. ERASMUS FRANS F.
012 567 7791
012 567 7466
MBChB

Appendix G:

Permission letter to Dr Frans Erasmus Diabetes Clinic for access to patient files and records

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Permission to access Records / Files / Database at the

Dr Frans Erasmus Diabetes Clinic

To: Dr Frans Erasmus
Diabetes Clinic
29 Jan Booysen Street
Annlin
Pretoria
0182

From: Lucresia Kruger
Department of Speech-Language Pathology and Audiology

Re: Permission to do research at the Dr Frans Erasmus Diabetes Clinic

The title of the study is: **Auditory Neural function of normal hearing adults with Type 2 Diabetes Mellitus.**

The study is approved by the relevant Head of Department (HOD),
Dr Jeannie van der Linde

Dr Leigh Biagio de Jager, Prof Paul Rheeder and I are researchers; I am requesting permission on behalf of all of us to conduct a research study on your patients with Type 2 Diabetes Mellitus. We will also require access to the patient files, their permission is requested in the participant consent form to use their clinical information documented in their file.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No.2 of 2000.

The researcher request access to the following information:

-Patients who have Type 2 Diabetes Mellitus

-The patient's clinical files

We intend to publish the results of the research study in a professional journal and/or at meetings like symposia, congresses, or other meetings of such nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We will not proceed with the research study until we have received approval from the Faculty of Health Science Research Ethics Committee – University of Pretoria.

Yours Sincerely,

Lucresia Kruger
Principal Investigator
Email: lucresiak@gmail.com

PERMISSION TO CONDUCT THE ABOVE RESEARCH STUDY AT THIS CLINIC AND TO ACCESS THE INFORMATION AS REQUESTED, IS HEREBY APPROVED, ON CONDITION THAT THERE WILL BE NO COST TO THE CLINIC

Dr Frans Erasmus
Owner
Dr Frans Erasmus Diabetic Clinic

6/3/2018.
Date

DR. F.F. ERASMUS
PR. No. 149 2373
29 JAN BOOYSEN ST.
ANNLIN
0129

DR. ERASMUS FRANS F.
012 567 7791
012 567 7466
MBChB

Appendix H:

Permission letter to Drs. Joynt, Venter & van Rensburg and associates at Park Medical Centre

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

LETTER TO REQUEST PERMISSION FROM THE CLINIC

Dr's Joynt Venter Van Rensburg and Associates Park Medical Centre

April 2018

Dr van Rensburg
Dr's Joynt Venter Van Rensburg and Associates Park Medical Centre
P. O. Box 154
Witbank
1035

Dear Dr van Rensburg

APPLICATION FOR PERMISSION TO CONDUCT A RESEARCH STUDY

I, Lucresia Kruger (Student number: 14039789) will be conducting a research study in 2018 for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology-University of Pretoria. I hereby request permission to conduct my research study at the Joynt, Venter, van Rensburg and associate's diabetes clinic. If permission is granted, I plant to start with collection from April 2018.

The title of my study is: **AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS**

This study will aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. The results of the current study can assist researchers in better determining subtle auditory neurological changes in individuals with Type 2 Diabetes Mellitus compared to healthy participants. If any audiological problems are identified in the participants I will provide them with the results and a referral letter to the Department of Speech-Language Pathology and Audiology at the University of Pretoria or any other private Audiologist for further investigation should they wish to do so.

Thank you for considering this request.

If you require any further information, contact:
Lucresia Kruger (student researcher)
at lucresiak@gmail.com or 084 626 8585.

Sincerely,

Lucresia Kruger
Student Researcher

Dr Leigh Biagio de Jager
Supervising Researcher

Dr's Joynt, Venter & Ass.
P.O. Box 154
Witbank
1035

I, hereby give written permission for the researchers to conduct this research study at Joynt, Venter, van Rensburg and associates.

.

Dr van Rensburg
Head of Joynt, Venter, van Rensburg and associates clinic

Appendix I:

Permission letter to Drs. Joynt, Venter & van Rensburg and associates at Park Medical Centre for access to patient files and records

Permission to access Records / Files / Database at the

Dr's Joynt, Venter, Van Rensburg and Associates

To: Dr Van Rensburg
Dr's Joynt, Venter, Van Rensburg and Associates Park Medical Centre
P. O. Box 154
Witbank
1035

From: Lucresia Kruger
Department of Speech-Language Pathology and Audiology

Re: Permission to do research at Dr Joynt, Venter, Van Rensburg and Associates Park Medical Centre

The title of the study is: **Auditory Neural function of normal hearing adults with Type 2 Diabetes Mellitus.**

The study is approved by the relevant Head of Department (HOD),
Dr Jeannie van der Linde

Dr Leigh Biagio de Jager, Prof Paul Rheeder and I are researchers; I am requesting permission on behalf of all of us to conduct a research study on your patients with Type 2 Diabetes Mellitus. We will also require access to the patient files, their permission is requested in the participant consent form to use their clinical information documented in their file.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No.2 of 2000.

The researcher request access to the following information:

-Patients who have Type 2 Diabetes Mellitus

-The patient's clinical files

We intend to publish the results of the research study in a professional journal and/or at meetings like symposia, congresses, or other meetings of such nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We will not proceed with the research study until we have received approval from the Faculty of Health Science Research Ethics Committee – University of Pretoria.

Yours Sincerely,

Lucresia Kruger
Principal Investigator
Email: lucresiak@gmail.com

Dr's Joynt, Venter & Ass.
P.O. Box 134
Witbank
1035

PERMISSION TO CONDUCT THE ABOVE RESEARCH STUDY AT THIS CLINIC AND TO ACCESS THE INFORMATION AS REQUESTED, IS HEREBY APPROVED, ON CONDITION THAT THERE WILL BE NO COST TO THE CLINIC

Dr Van Rensburg
Dr's Joynt Venter Van Rensburg and Associates

6/4/2018
Date

Appendix J:

World Medical Association Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

Appendix K:

Type 2 Diabetes Mellitus participant information letter and informed consent form

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

INFOMRATION LEAFLET AND INFORMED CONSENT FOR TYPE 2 DIABETES MELLITUS PARTICIPANTS

AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

January 2018

Dear Participant,

1) INTRODUCTION

You are invited to volunteer for a research study that I am conducting for a Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask me Lucresia Kruger at 084 626 8585. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

The main aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. An age and gender matched control group will also be included in the study and will consist of participants without diabetes mellitus.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You will undergo a single assessment lasting a minimum of 1-1 ½ hours at the Diabetic Clinic of Steve Biko Academic Hospital . I will collect clinical information from your hospital file and the following procedures will be included in the assessment: Accu-Check Blood glucose monitoring system, hearing tests and Auditory Brainstem Response measurements.

Summary of the tests that will be used in this research study:

Assessment category	Test	Expected from participant
Medical Tests	Accu-Check Blood glucose monitoring system	A small prick will be made on your finger and the blood will then be inserted into the Accu-Check Blood glucose monitoring system to ensure your blood glucose levels are within normal limits. This test might be of some discomfort
Auditory Tests	Otoscopy	Inspection of the ear canal and eardrum with a otoscope, while you are seated upright
	Acoustic Immitance Measurements	You will not have to respond in any way, a soft probe will be inserted into the ear canal while you are seated upright. Some pressure build up will occur and loud sounds will be presented
	Pure tone Audiometry	You will be required to press a button when a beep sound is heard trough earphones
	Auditory Brainstem Response (ABR) testing	You will not have to respond in any way, electrodes will be placed on and around the head and neck area and a soft probe inserted in your ear while you are lying on a bed

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study. The assessment does have a long duration and the participant may experience some discomfort or fatigue, however the objective measure that will be performed do give you time to relax and even sleep which is recommended as no response from you is necessary. Some discomfort might be experienced when assessing the blood glucose levels but will be done quickly and effectively.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If a hearing problem is identified, you will be referred to the Department of Speech-Language Pathology and Audiology for further investigation with a referral letter summarising your results.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this research study is voluntary. You can withdraw from the study at any time; data already collected will be excluded from the study. *This will not affect your treatment at the Diabetic Clinic of Steve Biko Academic Hospital.*

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria. *Should you require any further information you can contact them at 012 356 3084 or 012 356 3085*

8) INFORMATION AND CONTACT PERSON

The contact person for this study is Ms Lucresia Kruger. If you have any questions about the study feel free to contact me at 084 626 6585 or at lucresiak@gmail.com. Alternatively you can contact my supervisor Prof Bart Vinck at Bart.Vinck@up.ac.za or my co-supervisor Dr Leigh

Blaglo de Jager at leigh.blaglo@up.ac.za or Prof Paul Rheeder at paul.rheeder@med.up.ac.za.

9) COMPENSATION

You will not be paid for participating in the study; no extra costs are expected to be concurred by you.

10) CONFIDENTIALITY:

Personal information from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be used in a scientific article and dissertation which will be made available within the field of audiology.
All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I hereby agree to participate in the above mentioned research project. I have read the above information and understand what is required of me in this research study. I acknowledge that my results may be used anonymously for research purposes. I am aware that I participate voluntarily and that I may withdraw from the research study at any time.
I have received a signed copy of this informed consent agreement.

_____
Participant name

_____ _____
Participant signature Date

_____
Investigator's name

_____ _____
Investigator's signature Date

Witness name and signature _____ Date _____

VERBAL INFORMED CONSENT

I, the undersigned, have read and explained fully to the participant the information leaflet, which explains the nature, process, risks, discomforts and benefits of the study, in which I have asked the participant to participate in.

The participant acknowledges that the results may be used anonymously for research purposes. The participant indicates that she/he understand what is expected of them. She/he understands that there is no penalty should she/he wish to withdraw from the study. This withdrawal will have no effect on his/her medical treatment in any way. I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Person seeking consent _____
(Please print)

Signature _____ Date _____

Witness's name _____
(Please print)

Signature _____ Date _____

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Appendix L:

Control group participant information letter and informed consent form

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

CONTROL GROUP PARTICIPANT INFOMRATION LEAFLET AND INFORMED CONSENT

AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

January 2018

Dear Participant,

1) INTRODUCTION

You are invited to volunteer for a research study that I am conducting for a Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask me Lucresia Kruger at 084 626 8585. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

The main aim of my study is to describe the auditory neural function of adults with Type 2 Diabetes Mellitus by means of Auditory Brainstem Responses with various stimulation rates, presenting with normal behavioural audiometric thresholds. An age and gender matched control group will also be included in the study and will consist of participants without diabetes mellitus.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You will undergo a single assessment lasting a minimum of 1-1 ½ hours at the Diabetic Clinic of Steve Biko Academic Hospital . I will collect clinical information from your hospital file and the following procedures will be included in the assessment: Accu-Check Blood glucose monitoring system, hearing tests and Auditory Brainstem Response measurements.

Summary of the tests that will be used in this research study:

Assessment category	Test	Expected from participant
Medical Tests	Accu-Check Blood glucose monitoring system	A small prick will be made on your finger and the blood will then be inserted into the Accu-Check Blood glucose monitoring system to ensure your blood glucose levels are within normal limits. This test might be of some discomfort
Auditory Tests	Otoscopy	Inspection of the ear canal and eardrum with a otoscope, while you are seated upright
	Acoustic Immitance Measurements	You will not have to respond in any way, a soft probe will be inserted into the ear canal while you are seated upright. Some pressure build up will occur and loud sounds will be presented
	Pure tone Audiometry	You will be required to press a button when a beep sound is heard trough earphones
	Auditory Brainstem Response (ABR) testing	You will not have to respond in any way, electrodes will be placed on and around the head and neck area and a soft probe inserted in your ear while you are lying on a bed

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study. The assessment does have a long duration and the participant may experience some discomfort or fatigue, however the objective measure that will be performed do give you time to relax and even sleep which is recommended as no response from you is necessary. Some discomfort might be experienced when assessing the blood glucose levels but will be done quickly and effectively.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If a hearing problem is identified, you will be referred to the Department of Speech-Language Pathology and Audiology for further investigation with a referral letter summarising your results.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this research study is voluntary. You can withdraw from the study at any time; data already collected will be excluded from the study. *This will not affect your treatment at the Diabetic Clinic of Steve Biko Academic Hospital.*

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria. *Should you require further information you can contact them at 012 356 3084 or 012 356 3085.*

8) INFORMATION AND CONTACT PERSON

The contact person for this study is Ms Lucresia Kruger. If you have any questions about the

study feel free to contact me at 084 626 8585 or at lucresiak@gmail.com. Alternatively you can contact my supervisor Prof Bart Vinck at Bart.Vinck@up.ac.za or my co-supervisor Dr Leigh Blaglo de Jager at leigh.blaglo@up.ac.za or Prof Paul Rheeder at paul.rheeder@med.up.ac.za.

9) COMPENSATION

You will not be paid for participating in the study; no extra costs are expected to be concurred by you.

10) CONFIDENTIALITY:

Personal information from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be used in a scientific article and dissertation which will be made available within the field of audiology.
All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I hereby agree to participate in the above mentioned research project. I have read the above information and understand what is required of me in this research study. I acknowledge that my results may be used anonymously for research purposes. I am aware that I participate voluntarily and that I may withdraw from the research study at any time.
I have received a signed copy of this informed consent agreement.

_____
Participant name

_____ _____
Participant signature Date

_____
Investigator's name

_____ _____
Investigator's signature Date

Witness name and signature _____ Date _____

VERBAL INFORMED CONSENT

I, the undersigned, have read and explained fully to the participant the information leaflet, which explains the nature, process, risks, discomforts and benefits of the study, in which I have asked the participant to participate in.

The participant acknowledges that the results may be used anonymously for research purposes. The participant indicates that she/he understand what is expected of them. She/he understands that there is no penalty should she/he wish to withdraw from the study. This withdrawal will have no effect on his/her medical treatment in any way. I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Person seeking consent _____
(Please print)

Signature _____ Date _____

Witness's name _____
(Please print)

Signature _____ Date _____

Appendix M:

Data capturing sheet for participants with Type 2 Diabetes Mellitus

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

DATA CAPTURING SHEET FOR PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS

AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

Informed consent signed and received: ☐ **Numerical code:** _____

Blood glucose level: _____

Date of testing: _____

Age: _____ **Gender: Male** ☐ **Female** ☐

Duration of T2DM:

_____

Age of diagnoses:

_____

Medication used for T2DM:

_____

_____

_____

Other medications used:

_____

_____

_____

Any other diseases/disorders:

_____

_____

Do you smoke or use alchol:

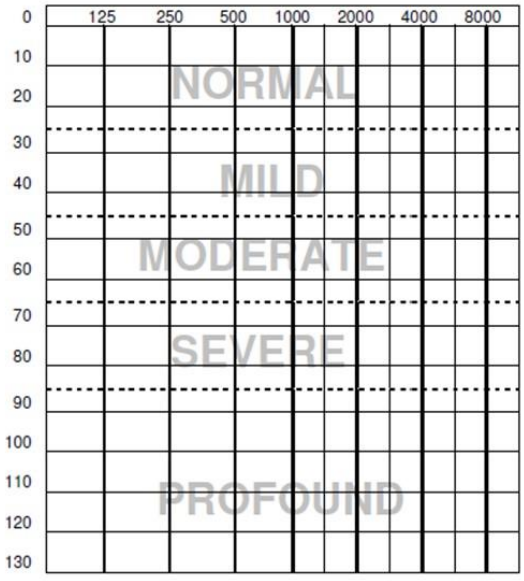
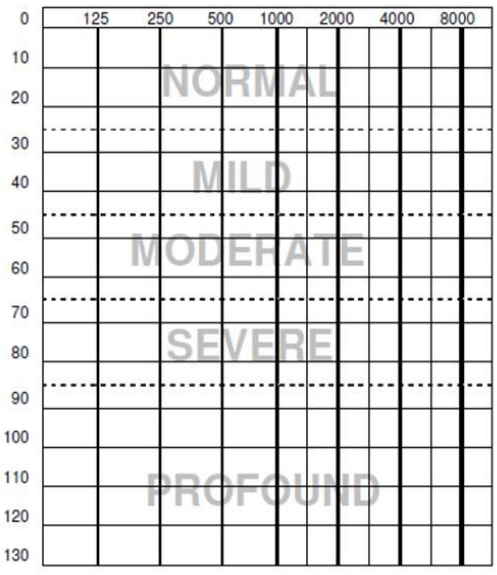
_____

_____

Past/present exposure to loud noise, head trauma or neurological conditions or family history of ear related pathologies :

_____

_____

Audiometric Results		
Procedure	**Right**	**Left**
Otoscopy		
Acoustic Immittance Measures	Tympanogram type: _____ Ear canal pressure:_____daPa Static compliancence: _____ml Ear canal volume: _____ml	Tympanogram type: _____ Ear canal pressure:____daPa Static compliancence: ____ml Ear canal volume: _____ml
Screening ipsi-lateral acoustic reflexes	500 Hz: _____ dB 1000 Hz: _____ dB 2000 Hz: _____ dB 4000 Hz: _____ dB	500 Hz: _____ dB 1000 Hz: _____ dB 2000 Hz: _____ dB 4000 Hz: _____ dB
Pure tone audiometry	PTA: _____dB HL *Regteroor / Right Ear* 	PTA: _____dB HL *Linkeroor / Left Ear* 
Auditory	**Sandard ABR protocol**	

<table>
<tr><td rowspan="2">Brainstem Response (ABR)</td><td><u>Abselute latencies:</u>
Wave I: _____ms
Wave III: _____ms
Wave V: _____ms
<u>Interpeak latensies:</u>
Wave I-III: _____ms
Wave I-V: _____ms
Wave III-V: _____ms
<u>Amplitudes:</u>
Wave I: _____µV
Wave III: _____µV
Wave V: _____µV</td><td><u>Abselute latencies:</u>
Wave I: _____ms
Wave III: _____ms
Wave V: _____ms
<u>Interpeak latensies:</u>
Wave I-III: _____ms
Wave I-V: _____ms
Wave III-V: _____ms
<u>Amplitudes:</u>
Wave I: _____µV
Wave III: _____µV
Wave V: _____µV</td></tr>
<tr><td colspan="2">Faster rate ABR protocol</td></tr>
<tr><td></td><td><u>Abselute latencies:</u>
Rate 45.1 Hz Wave V: _____ms
Rate 61.1 Hz Wave V: _____ms

<u>Amplitudes:</u>
Rate 45.1 Hz Wave V: _____µV
Rate 61.1 Hz Wave V: _____µV</td><td><u>Abselute latencies:</u>
Rate 45.1 Hz Wave V: _____ms
Rate 61.1 Hz Wave V: _____ms

<u>Amplitudes:</u>
Rate 45.1 Hz Wave V: _____µV
Rate 61.1 Hz Wave V: _____µV</td></tr>
</table>

_____ _____

Researcher's signature Date

Lucresia Kruger

_____ _____

1. Independent professional name and signature Date

_____ _____

2. Independent professional name and signature Date

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Appendix N:

Data capturing sheet for control group participants

DATA CAPTURING SHEET FOR CONTROL GROUP PARTICIPANTS

AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

Informed consent signed and received: ☐ **Numerical code: _____**

Blood glucose level: _____

Date of testing: _____

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Age: _____ **Gender: Male** ☐ **Female** ☐

Other medications used:

_____

_____

_____

Any other diseases/disorders:

_____

_____ **Do you smoke or use alchol:**

_____

_____

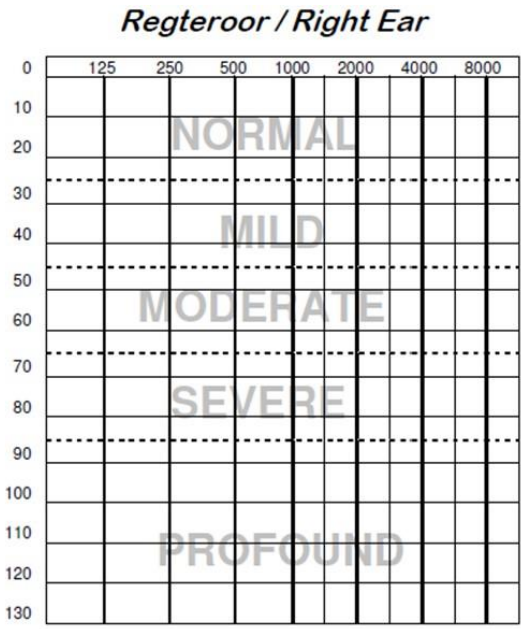
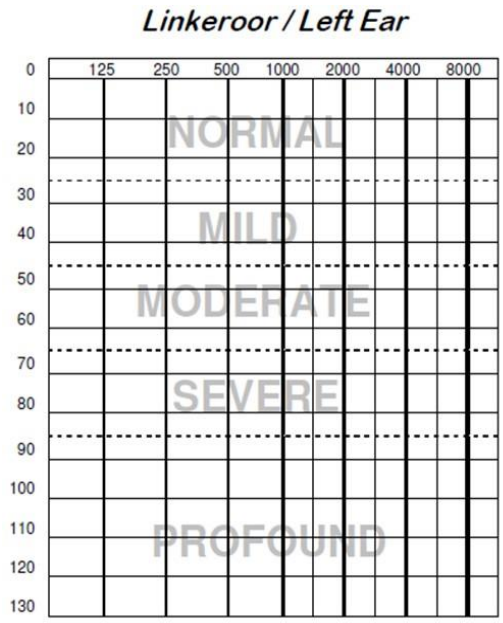
Past/present exposure to loud noise, head trauma or neurological conditions or family history of ear related pathologies :

_____

_____

Faculty of Humanities
Department of Speech-Language Pathology and Audiology
Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

Audiometric Results		
Procedure	**Right**	**Left**
Otoscopy		
Acoustic Immittance Measures	Tympanogram type: _____ Ear canal pressure:_____daPa Static compliancence: _____ml	Tympanogram type: _____ Ear canal pressure:____daPa Static compliancence: ____ml

	Ear canal volume: _____ml	Ear canal volume: _____ml
Screening ipsi-lateral acoustic reflexes	500 Hz: _____ dB 1000 Hz: _____ dB 2000 Hz: _____ dB 4000 Hz: _____ dB	500 Hz: _____ dB 1000 Hz: _____ dB 2000 Hz: _____ dB 4000 Hz: _____ dB
Pure tone audiometry	PTA: _____dB HL 	PTA: _____dB HL 
Auditory Brainstem Response (ABR)	**Sandard ABR protocol**	
	<u>Abselute latencies:</u> Wave I: _____ms Wave III: _____ms Wave V: _____ms <u>Interpeak latensies:</u> Wave I-III: _____ms Wave I-V: _____ms Wave III-V: _____ms <u>Amplitudes:</u> Wave I: _____µV Wave III: _____µV Wave V: _____µV	<u>Abselute latencies:</u> Wave I: _____ms Wave III: _____ms Wave V: _____ms <u>Interpeak latensies:</u> Wave I-III: _____ms Wave I-V: _____ms Wave III-V: _____ms <u>Amplitudes:</u> Wave I: _____µV Wave III: _____µV Wave V: _____µV
	Faster rate ABR protocol	

	<u>Abselute latencies:</u> Rate 45.1 Hz Wave V: _____ms Rate 61.1 Hz Wave V: _____ms <u>Amplitudes:</u> Rate 45.1 Hz Wave V: _____µV Rate 61.1 Hz Wave V: _____µV	<u>Abselute latencies:</u> Rate 45.1 Hz Wave V: _____ms Rate 61.1 Hz Wave V: _____ms <u>Amplitudes:</u> Rate 45.1 Hz Wave V: _____µV Rate 61.1 Hz Wave V: _____µV

_____ _____

Researcher's signature Date

Lucresia Kruger

_____ _____

1. Independent professional name and signature Date

_____ _____

2. Independent professional name and signature Date

Appendix O:

Participant's summary of results (Referral letter)

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

PARTICIPANT'S SUMMARY OF RESULTS (REFERRAL LETTER)

AUDITORY NEURAL FUNCTION OF NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

January 2018

Dear Participant,

Thank you for participating in the research study for my Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, University of Pretoria.

EXPLANATION OF PROCEDURES FOLLOWED AND YOUR RESULTS

You underwent a single assessment each contributing to the data collection for my study. Your results that will be used in this research study is recorded on the data capturing sheets attached to this letter.

Your results indicate:

☐ Normal results and no need for further audiological intervention (should you feel there is any changes in your hearing abilities please have your hearing reassessed, an annual hearing assessment is also recommended)

☐ Hearing difficulties/changes idicated by one or more of the assessments done in this study and follow up audiological intervention is reccomended.

Should any of the following be indicated **YES** by the researcher please follow up with the medical professional mentioned below:

Yes /No	Audiological difficullty	Medical professional to follow up with	Notes
☐Yes ☐No	Very low blood glucose level	General practitioner (clinic) if not currently diagnosed with diabetes mellitus or the Diabetes Clinic Staff at Steve Biko Academic Hospital if curently a patient there	
☐Yes ☐No	Abnormal Acoustic Immitance measures and/or Screening reflexes	Genereal practitioner (clinic) Ear, Nose and Throat specialist (Clinic)	
☐Yes ☐No	Abnormal pure tone audiometry (with normal acoustic immitance measures)	Audiologist- at the Department of Speech-Language Pathology and Audiology at the University of Pretoria (012 420 2357)	
☐Yes ☐No	Abnormal ABR results (with nprmal/abnormal pure tone results)	Audiologist- at the Department of Speech-Language Pathology and Audiology at the University of Pretoria (012 420 2357)	

INFORMATION AND CONTACT PERSON

Personal information from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be used in a scientific article and dissertation which will be made available within the field of audiology.

All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

The contact persons for this study is Ms Lucresia Kruger. If you have any questions about the studies feel free to contact us at lucresiak@gmail.com . Alternatively you can contact my supervisor Dr Leigh Biagio de Jager at leigh.biagio@up.ac.za.

_____ _____

Researcher's signature Date

Lucresia Kruger

Appendix P:

Declaration for the storage of research data and/or documents

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Principal Investigator's Declaration for the storage of research data and/or documents

I, the Principal Investigator(s), Lucresia Kruger of the following trial/study titled:

AUDITORY NEURAL FUNCTION ON NORMAL HEARING ADULTS WITH TYPE 2 DIABETES MELLITUS

_____

will be storing all the research data and/or documents referring to the above-mentioned trial/study at the following non-residential address:
Department of Speech-Language Pathology and Audiology
University of Pretoria
Corner of Lynnwood Road and Roper Street
Hatfield
South Africa

I understand that the storage for the abovementioned data and/or documents must be maintained for a minimum of <u>15 years</u> from the end of this trial/study.

Start date of the study: January 2018

Anticipated end date of study: September 2018

Year until which data will be stored: 2033

_____

_____ _____

Principal Researcher Date
Lucresia Kruger

_____

Dr Leigh Biagio de Jager Date
Research supervisor

Appendix Q:

Declaration of originality

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Faculty of Humanities
Department of Speech-Language Pathology and Audiology

DECLARATION OF ORIGINALITY

UNIVERSITY OF PRETORIA

The Department of **Speech-Language Pathology and Audiology** places great emphasis upon integrity and ethical conduct in the preparation of all written work submitted for academic evaluation.

While academic staff teaches you about referencing techniques and how to avoid plagiarism, you too have a responsibility in this regard. If you are at any stage uncertain as to what is required, you should speak to your lecturer before any written work is submitted.

You are guilty of plagiarism if you copy something from another author's work (e.g. a book, an article or a website) without acknowledging the source and pass it off as your own. In effect, you are stealing something that belongs to someone else. This is not only the case when you copy work word-for-word (verbatim), but also when you submit someone else's work in a slightly altered form (paraphrase) or use a line of argument without acknowledging it. You are not allowed to use work previously produced by another student. You are also not allowed to let anybody copy your work with the intention of passing it off as his/her work.

Students who commit plagiarism will not be given any credit for plagiarised work. The matter may also be referred to the Disciplinary Committee (Students) for a ruling.

Plagiarism is regarded as a serious contravention of the University's rules and can lead to expulsion from the University.

The declaration which follows must accompany all written work submitted while you are a student of the Department of **Speech-Language Pathology and Audiology**. No written work will be accepted unless the declaration has been completed and attached.

Full names of student: **Lucresia Kruger**

Student number: **14039789**

The topic of work: **Auditory neural function in normal hearing adults with Type 2**

Diabetes mellitus

Declaration

1. I understand what plagiarism is and am aware of the University's policy in this regard.
2. I declare that this **dissertation** (E.g. essay, report, project, assignment, dissertation, thesis, etc.) is my own original work. Where other people's work has been used (either from a printed source, Internet or any other source), this has been properly acknowledged and referenced in accordance with departmental requirements.
3. I have not used work previously produced by another student or any other person to hand in as my own.
4. I have not allowed, and will not allow, anyone, to copy my work with the intention of passing it off as his or her own work.

SIGNATURE:

Appendix R:

Letter of clearance from the Biostatistician

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LETTER OF CLEARANCE FOR STATISTICS

Auditory neural function of normal hearing adults with type 2 diabetes mellitus.

Lucresia Kruger
For MA Audiology

I hereby confirm that I am aware of the project and will undertake to assist with the statistical analysis of the data generated from the project.

The Data Analyses will consist of

- Descriptive statistics (means, medians, standard deviation and range, numbers and percentages)
- 2 Group comparisons will be made using the appropriate statistics for data (continuous and categorical) taking into account that data was matched at an individual level, for example, Wilcoxon matched pairs test or the McNemar test.

Sample size

- A sample size of 30 participants in each group allows detection of differences between 1 and ½ standard deviation with 80% power and alpha set at 0.05. It will also detect a difference in proportions of 20% or more.

Name _____**Prof P Rheeder**_____

Signature _____ _____

Date _____**29 November 2018**_____

Appendix S:

Submission confirmation for research article to Journal of American Academy of Audiology

Journal of the American Academy of Audiology

Submission Confirmation

Print

Thank you for your submission

Submitted to
Journal of the American Academy of Audiology

Manuscript ID
18-094

Title
Auditory neural function of normal hearing adults with Type 2 Diabetes Mellitus

Authors
Kruger, Lucresia
Blaglo De Jager, Leigh
Rheeder, Paul

Date Submitted
26-Nov-2018

Author Dashboard