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P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus

by

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A dissertation submitted in fulfilment of the requirements for the degree MA (Audiology)

in the Department of Speech-Language Pathology and Audiology at the

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I hope I have made all of you proud…

Abstract

Background: P300 event-related potentials can be used to measure auditory processing speed, working memory and attention.

Purpose: The purpose of the study was to compare latencies and amplitudes of the P300 event-related potentials in normal hearing adults with the latencies and amplitudes of participants diagnosed with type II Diabetes Mellitus (DM).

Research design: A two group (with diabetes and controls) comparative study (age- and sex-matched) with a non-probability sampling method was used.

Study sample: Sixty-four participants (32 adults with diabetes, 32 adults without diabetes) between the ages of 23 to 60 years participated (M 47.50 years, 10).

Data collection and analysis: Pure tone audiometry was performed to ensure participants had a pure tone average of ≤ 25 dB HL. The Folstein Mini-Mental State Examination was conducted which ensured participants had no cognitive impairment. Blood glucose levels were measured immediately prior to P300 testing. Amplitude and latency results were captured for the P300 test. Descriptive analysis was used to calculate the mean, standard deviation, as well as the median and 25^{th} and 75^{th} percentiles. In order to study the differences between adults with and without diabetes as well the effect of glucose, linear mixed model regression analyses were performed when left and right ears were combined, and simple linear regression when left and right ears were analysed separately.

Results: For the P300 latency results, a significant statistical difference (p<0.001) was observed between the participants with diabetes (352.46 ms, SD 36.36) and participants without diabetes (314.09 ms, SD 32.08). A significant statistical difference (p<0.001) in amplitude was also observed between the participants with diabetes (12.10 µV, SD 3.70) and participants without diabetes (15.08 µV, SD 2.82). Glucose was a key moderator of amplitude but not latency after adjusting for diabetes status. Glucose had no effect on amplitude and latency for adults without type II DM.

Conclusions: It was found that type II DM decreases P300 amplitude and increases latency. In adults with type II DM, attention and working memory, as denoted by P300 amplitude, may deteriorate with an increase in glucose levels on the day of testing.

Keywords

Type II Diabetes Mellitus

Information processing speed

Hippocampus

P300

Amplitude

Latency

Glucose

Attention

Working memory

Event-related potential

List of abbreviations

AEP	**-**	Auditory Evoked Potential
CNS	**-**	Central Nervous System
dB	**-**	decibels
dBHL	**-**	decibel Hearing Level
dBnHL	**-**	decibel normal Hearing Level
dBSPL	**-**	decibel Sound Pressure Level
DM	**-**	Diabetes Mellitus
ERP	**-**	Evoked Response Potentials
Folstein MMSE	**-**	Folstein Mini Mental State Exam
Fpz	-	Low forehead
Fz	**-**	High Forehead
Hz	**-**	Hertz (frequency)
µV	**-**	Microvolt
m	**-**	mean
mmol/L	**-**	millimoles per litre
ms	**-**	milliseconds
nHL	**-**	normal Hearing Level
ppeSPL	**-**	peak to peak equivalent Sound Pressure Level
SE	-	Standard Error
SD	-	Standard Deviation
TBI	**-**	Traumatic Brain Injury

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Student number: **14064066**

The topic of work: **P300 event related potentials in normal hearing adults with type 2 Diabetes Mellitus**

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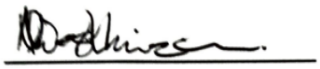

Special Communication

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.

CHAPTER 1

INTRODUCTION

1.1. Diabetes Mellitus

Interest on the impact of Diabetes Mellitus (DM) on cognitive function in individuals is increasing as the incidence of DM has increased in recent years. This increase of DM occurs due to an increase in longevity, urbanisation, obesity and changes in the lifestyle of the population (Andreadou, Mitrakou, Constantinides, & Triantafyllou, 2012; Heydari, Radi, Razmjou, & Amiri, 2010; International Diabetes Federation, 2017). It was estimated that between 2010 and 2025 the occurrence rate of DM will have increased by 50% (Heydari et al., 2010). A recent report suggested that in Africa there are approximately 14.7 million individuals who have DM, yet about 78% of the African population are undiagnosed (International Diabetes Federation, 2017).

DM is a metabolic disorder with multiple aetiologies, characterised by prolonged hyperglycaemia together with high blood glucose levels including disturbances of fat, protein and carbohydrate metabolism that results from deficiencies in insulin secretions and/or insulin action (Alberti & Zimmet, 1998; American Diabetes Association, 2004; Bajaj, Puthuchery, Bhat, & Ranjan, 2014). DM results from complete or relative insulin deficiency (Lisowska, Namysłowski, Morawski, & Strojek, 2001). There are multiple pathogenic processes involved in DM development. Some include the autoimmune destruction of the ß-cells of the pancreas together with insulin deficiency (American Diabetes Association, 2004). Inadequate insulin secretion and/or diminished tissue responses to insulin causes deficient insulin action (American Diabetes Association, 2004).

Individuals diagnosed with DM experience long-term damage, failure and dysfunction of various organs (Alberti & Zimmet, 1998; American Diabetes Association, 2004; Bajaj et al., 2014). Symptoms experienced by individuals with DM such as blurry vision, thirst, weight loss and polyuria may not be severe, or may even be absent, which will result in functional and pathological changes before a diagnosis is made (Alberti & Zimmet, 1998). Nervous tissue within the human body is dependent on glucose levels that are stable. If the patient has hypoglycaemia for an extended period of time it can cause neurological problems (Alvarenga et al., 2005). Individuals with DM are also at an increased risk for cerebrovascular, cardiovascular and peripheral vascular disease (Alberti & Zimmet, 1998; Wrighten, Piroli, Grillo, & Reagan, 2008). The brain undergoes structural changes that increase the risk of cognitive decline

including attention, memory, psychomotor speed and executive function (Hamed et al., 2013). In the long term, DM may cause cerebral disorders as a result of changes in the cerebral blood supply (Biessels, Kappelle, Bravenboer, Erkelens, & Gispen, 1994).

DM falls into two etiopathogenetic categories. The first of the two categories is type I DM which is caused by an absolute deficiency of insulin secretion (American Diabetes Association, 2004). Type I DM occurs when the body cannot produce adequate levels of insulin in order to maintain a normal blood glucose level (Mishra, Sanju, & Kumar, 2015). Patients with type I DM share certain cognitive deficits, including a decline in psychomotor efficiency and a slowing in information processing speed (Kodl & Seaquist, 2008). Other problems include deficits in attention, memory, executive function, motor speed, vocabulary and general intelligence (Kodl & Seaquist, 2008; Wrighten et al., 2008). Type I DM may be associated with neural degeneration. The myelin sheath of the vestibulocochlear nerve may also degenerate (Mohammadkhani, Jalilzadeh, Jalaei, Nasli, & Majidi, 2013).

Type II DM is caused by an inadequate compensatory insulin secretory response and a resistance to insulin action (American Diabetes Association, 2004; Mishra et al., 2015). As with type I DM, type II DM is also associated with impaired cognitive processes (Biessels et al., 1994; Hissa, D'Almeida, Cremasco, & De-Bruin, 2002; Kodl & Seaquist, 2008; Messier, 2005; Ruis et al., 2009). Cognitive impairments in type II DM are characterised by a decline in executive functions, processing and psychomotor speed, verbal memory and fluency, complex motor function, delayed and immediate recall and attention (Kodl & Seaquist, 2008; Ruis et al., 2009; Wrighten et al., 2008). In addition, individuals of a more advanced age of more than 60 to 65 years appear to have more cognitive deficits (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). In South Africa, the majority of individuals with DM are diagnosed with type II DM (International Diabetes Federation, 2017). Individuals later diagnosed with type II DM may have been asymptomatic for a few years before their initial diagnosis (Alberti & Zimmet, 1998). Some of the long-term effects of DM are not only retinopathy, blindness, nephropathy that can cause renal failure, neuropathy with the risk of foot ulcers and amputation but also hearing loss (Alberti & Zimmet, 1998; Mozaffari, Tajik, Ariaei, Ali-Ehyaii, & Behnam, 2010).

1.2. Diabetes Mellitus effects on hearing sensitivity

Hearing loss is a health problem that influences an individual's work productivity, social interactions, functional status, well-being and quality of life (Hong, Buss, & Thomas, 2013). The link between DM and hearing sensitivity has been widely reported and is on the increase (Bajaj et al., 2014; Calvin & Watley, 2015; Helzner & Contrera, 2016; Prabhu & Shanthala, 2016; Rajamani, Senniappan, & Radhakrishnan, 2018; Xipeng et al., 2013). Hearing loss as a result of type II DM affects structural and functional elements of auditory perception, reception and reaction (Pandey & Pandey, 2016). Hearing loss has been found to be related to the duration of type II DM (Prabhu & Shanthala, 2016).

A hearing loss is defined as having a hearing impairment and a pure tone average of 25 decibels (dB) or more in the affected ear. Patients diagnosed with type II DM typically present with a mild to moderate sloping sensorineural hearing loss (Frisina, Mapes, Kim, Frisina, & Frisina, 2006; Meena, Sonkhya, & Sonkhya, 2016; Morrison, Morar, Morrison, Purewal, & Weston, 2014; Ren et al., 2017). Other characteristics of hearing loss associated with type II DM is that the hearing loss is bilateral, progressive and gradual in onset (Rajamani et al., 2018).

Hearing loss in type II DM might be attributed to microangiopathic processes associated with thickening of the basement membrane (Hong et al., 2013; Misra, Agarwal, Bhatia, & Shukla, 2013). Within the cochlear structure in the lower and basal turns, loss of outer hair cells occurs (Mozaffari et al., 2010). In addition, type II DM affects the vasculature and neural systems of the inner ears leading to hearing loss (Calvin & Watley, 2015). Individuals diagnosed with type II DM might experience hearing loss due to less keratin (protein) lining the ear canal and tinnitus (Calvin & Watley, 2015; Rajamani et al., 2018). The nerves and vessels in the cochlea are also damaged by hyperglycaemia, which might lead to neural degeneration of the auditory system (Çayönü, Çapraz, Acar, Altundağ, & Salihoğlu, 2014). Complications of the auditory pathway might be from vascular and neural changes, loss of outer hair cells, or thickening of the capillary walls (Ren et al., 2017; Xipeng et al., 2013). In addition to peripheral hearing loss, central auditory processing skills are often affected by type II DM.

1.3. Diabetes Mellitus effects on central auditory processes

A complex metabolic disease such as DM has long-lasting effects on several organs of the human body including the eyes, heart and brain. These serious complications can be avoided in most cases by early diagnosis and treatment (International Diabetes Federation, 2017). An adequate supply of glucose is important for cerebral functioning (Schomer & Lopes da-Silva, 2011). DM is a known risk factor for cognitive dysfunction (Cukierman, Gerstein, & Williamson, 2005). Mild cognitive dysfunction is associated with both type I and type II DM, as DM effects sensory systems which damage cognitive processes (Hernández, Aguirre-manzo, Monteón, & Guadalupe, 2018). The chronic effects of type I DM ranges from a microscopic to macroscopic level and effects all the levels of the Central Nervous System (CNS) (Sadeghi, Hami, Razavi, Esfandiary, & Hejazi, 2016). Abnormalities such as decreased grey matter volumes and densities of the thalami, insular cortex, hippocampal, frontal gyri, superior and middle temporal gyri, temporal lobe sclerosis as well as a decline in white matter in the parahippocampal gyrus, frontal and temporal lobes can be found with macroscopic neuroimaging (Gold et al., 2007; Sadeghi et al., 2016). Neuronal changes such as increased cerebral microvascular permeability, synaptic and neuronal alterations and neuronal loss might cause cognitive impairment and increase the risk of developing dementia (Sadeghi et al., 2016). Some of the other CNS complications that results from both type I and type II DM are structural changes and/or atrophy of the brain, disrupted insulin signalling, and changes in the electrophysiological processes and properties of the brain which result in deficits in the individual's cognitive performance (Kurita, Katayama, & Mochio, 1996; Reagan, Grillo, & Piroli, 2009; Wrighten et al., 2008).

Type II DM affects several cognitive processes including auditory processing information due to a decline in the processing resources (Koekkoek, Kappelle, van den Berg, Rutten, & Biessels, 2015; Manschot et al., 2006; Messier, 2005; Sadeghi et al., 2016; Van Bussel et al., 2016). Type II DM has an effect on one of the most sensitive areas of the brain, namely the hippocampus (Sadeghi et al., 2016). This structure is horseshoe-shaped with one hippocampus being located in the right hemisphere of the brain and the other one located in the left hemisphere (Sadeghi et al., 2016). The hippocampus plays an important role in emotional, reproductive and

adaptive behaviour and memory formation (Sadeghi et al., 2016). The structural complexity of the hippocampus is vulnerable to various pathological conditions including DM (Sadeghi et al., 2016). The neurological consequence of type II DM is cognitive decline caused by rearrangement and changes to the electrophysiological properties of the hippocampal neurons as well as a reduction in the functional connectivity of the hippocampus leading to slower processing of information (Sadeghi et al., 2016; Wrighten et al., 2008; Zhou et al., 2010). With brain imaging results there was a decline in grey and white matter of the brain which was associated with reduced processing speed, executive function and memory (Koekkoek et al., 2015; Moheet, Mangia, & Seaquist, 2016).

The neuropsychological examination found that type II DM affects particularly memory, attention, information processing speed, executive function and repetition (Dey, Misra, Desai, Mahapatra, & Padma, 1997; Kodl & Seaquist, 2008; Manschot et al., 2006). Mishra et al. (2015) explored how auditory processing was impaired using a behavioural test of temporal resolution in individuals with type II DM (30 to 40 years of age) with a high-frequency hearing loss. This poor temporal resolution results obtained was attributed to a combination of changes that occurred in the central auditory nervous system and to the broadened auditory filters in the cochlea. This suggests that type ll DM has a detrimental effect on the auditory processing and temporal resolution of an individual (Mishra et al., 2015).

By using other methods such as auditory and temporal processing tests, it was found that auditory temporal processing and single tone loudness discrimination was diminished in individuals with type ll DM with no history of hearing disorders (McCrimmon, Deary, & Frier, 1997). This indicates that due to changes in the auditory centres of the brain, individuals will perform poorer on the Gap Detection Test (McCrimmon et al., 1997). To determine what effect controlled hypoglycaemia has on these two processes McCrimmon et al. (1997) conducted a study using simple auditory processing and temporal processing tests. The results of these tests indicated that perceived single tone loudness discrimination was diminished and that hypoglycaemia has a detrimental effect on auditory temporal processing (McCrimmon et al.,1997).

Cognitive skills are important for auditory discrimination, attention and information processing (Duarte et al., 2009). Even mild forms of cognitive dysfunction may affect daily activities which require certain cognitive domains such as processing speed, general intelligence, psychomotor efficiency, learning, memory, attention and executive function (Hazari, Ram Reddy, Uzma, & Santhosh Kumar, 2015; Ryan & Geckle, 2000; Sima, 2010; Stewart & Liolitsa, 1999). A shortage of glucose has an effect on brain processes including auditory temporal processing and simple auditory processing (McCrimmon et al., 1997). Therefore, diabetes research and care places an emphasis on the prevention and treatment of the complications which results from DM (Biessels et al., 1994). The correlation found between cognitive deficiencies and DM implies a need to monitor auditory health in DM patients (Diniz & Guida, 2009; Mochizuki, Oishi, Hayakawa, Matsuzaki, & Takasu, 1998).

The aforementioned provides evidence that both type I and type II DM are related to structural and functional changes in the brain where this was associated with reduced auditory processing speed, executive function and memory (Koekkoek et al., 2015; Moheet et al., 2016; Sadeghi et al., 2016). A neurophysiological test that can be used to determine the degree to which processing speed, executive function and memory are reduced by type II DM is P300 event-related potentials (Awad, Gagnon, & Messier, 2004; Wrighten et al., 2008).

1.4. P300 event-related potentials overview

The P300 event-related potential is a far-field non-invasive neurophysiological test offering an objective measure of temporal processing which was found to be useful in studies of auditory decision making, memory and information processing (Andreadou et al., 2012; Hazari et al., 2015; McPherson, 1996). The P300 reflects information processing and speed of neuronal events that is associated with memory and attention mechanisms and are dependent on internal cognitive processes (David, Finamor, & Buss, 2018; Kyizom, Singh, Singh, Tandon, & Kumar, 2010; Schomer & Lopes da-Silva, 2011; Somani & Shukla, 2014; Wrighten et al., 2008). P300 is known as an endogenous response and the response is dependent on internal cognitive events that are relatively independent of subject characteristics and the stimulus factors (Lombard, 2005). P300 is based on an “oddball” paradigm during which a response

is elicited when the participant attends to and detects a change in stimulus in a sequence of standard stimuli (frequent), from the other stimuli (infrequent) (Picton, 1992; Lombard, 2005). The difference between the frequent and infrequent stimulus will affect the latency, morphology, and amplitude of the response (Lombard, 2005).

The P300 response is defined as the largest peak occurring between 240 and 400ms (milliseconds) after stimulus onset where the oddball stimulus is presented randomly 20% of the time during testing (Cosway, Strachan, Dougall, Frier, & Deary, 2001; Lombard, 2005). The amplitude of the P300 wave is typically between 8 to 15 μV (microvolt) (McPherson, 1996). The P300 wave consists of two components the P300a and the P300b (Uvais, Nizamie, Das, Praharaj, & Ul Haq Katshu, 2018). The P300a is located at the functional level and is associated with the attention orienting complex. The P300b is associated with psychological constructs such as information processing, cognitive closure and context updating (Uvais et al., 2018). Figure 1 illustrates the two components of the P300 wave.

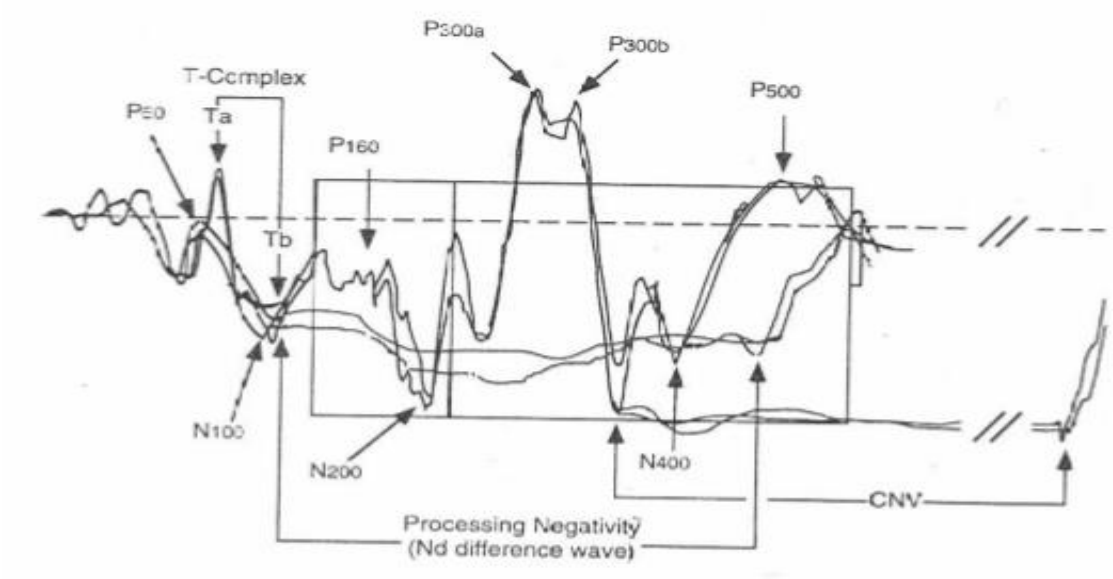

Figure 1: Illustration of the components of the P300: P300a and P300b (McPherson, 1996)

Different cognitive and neurophysiological processes are depicted through a variety of peaks/amplitudes within the 300 ms latency interval (Hall, 2007). The P300 provides information not only regarding the speed of neuronal events but of the efficiency of

higher cognitive processes and information processing such as short-term memory and attention (Cosway et al., 2001; Hazari et al., 2015; Thakur, Ray, Anand, & Panjwani, 2011). In broad terms, the latency component indicates the speed of processing and the amplitude relates to attentional ability (Cosway et al., 2001). The known neural generators of this late latency evoked potential, the P300 is said to be the hippocampus, frontal and temporal lobe, superior temporal gyri, thalamus, inferior parietal lobe, dorsolateral prefrontal cortex, cingulate cortex and amygdala (Kyizom et al., 2010; Lombard, 2005; McPherson, 1996; Schomer & Lopes da-Silva, 2011; Somani & Shukla, 2014; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015). As reported by Sadeghi et al. (2016), type II DM has a detrimental effect on the hippocampus resulting in the slower processing of information in adults with type II DM (Wrighten et al., 2008).

Clinically the P300 plays an important role in providing information regarding auditory processing (Picton, 1992). The P300 is useful in demonstrating the ability to discriminate between different stimuli even in the cases of sensory impairments (Picton, 1992). If there is some form of cognitive processing abnormalities the P300 wave will be delayed or small. The P300 wave, particularly the latency, is also used to indicate cognitive dysfunction in early cases of dementia and in the case of metabolic disorders such as DM (Picton, 1992).

1.5. P300 event-related potentials and Diabetes Mellitus

Type II DM causes cognitive changes of auditory learning, memory and attention that can be observed on the P300 wave in terms of latency and amplitude (Awad et al., 2004; Wrighten et al., 2008). Previous studies found that P300 latencies were increased in individuals who had been diagnosed with type ll DM (Alvarenga et al., 2005; Andreadou et al., 2012; Chen, Chen, Chen, & Luo, 2003; Cosway et al., 2001; Hamed et al., 2013; Hissa et al., 2002; Kurita et al., 1996; Mochizuki et al., 1998; Singh et al., 2013). The same was also true for both insulin and non-insulin dependent individuals with DM (Ryan & Geckle, 2000). This increase in the latencies of P300 shows that type ll DM causes delayed auditory temporal processing (Alvarenga et al., 2005).

P300 event-related potential is influenced by an increase in age leading to an increase in the latency and a decrease in the amplitude (Bourisly, 2016; Dinteren, Arns, Jongsma, & Kessels, 2014; Tsolaki et al., 2015). As increasing age (range: 56 to > 60 years) causes this aforementioned effect on the P300, it is not clear whether the following results obtained from the studies to follow was from type II DM and/or the participants' age as the researchers used participants above the age of 60 years. Alvarenga et al. (2005); Andreadou et al. (2012); Hissa et al. (2002); Cosway et al. (2001); Singh et al. (2013); Hazari et al. (2015); and Kurita et al. (1996) found that type II DM leads to an increase in latency and a decrease in P300 event-related potential. Two of the seven studies included participants up to the age of 65 years (Hazari et al., 2015; Kurita, Mochio, & Isogai, 1995). The remaining studies included participants of 70 years of age and older in their study population (Alvarenga et al., 2005; Andreadou et al., 2012; Cosway et al., 2001; Hissa et al., 2002; Singh et al., 2013).

In addition to age, it was found that individuals with a sensorineural and peripheral hearing loss presented with P300 waves with, smaller amplitudes and longer latencies yet several studies did not control for hearing loss (Reis et al., 2015; Reis & Iorio, 2007). Alvarenga et al. (2005) stated that they did not exclude individuals with a hearing loss. Alvarenga et al. (2005) and Hissa et al. (2002) did perform standard audiometric testing, but the researchers still included participants in the research studies who presented with a hearing loss. In the study by Hamed et al. (2013), participants did undergo standard audiometric testing but again researchers did not indicate whether they excluded participants that presented with a hearing loss. In addition, Cosway et al. (2001) and Tandon, Verma and Ram (1999) did not indicate whether they excluded participants if they had a hearing impairment or not. In the study conducted by Kurita et al. (1996), researchers indicated that they excluded individuals with a hearing impairment on the basis of lack of response to P300 stimuli at 70 dB. This suggests that participants with a mild to moderate loss were still included, however, the researchers did not do formal audiometric testing but ensured that stimuli were audible for P300 testing. Hazari et al. (2011) mentioned that they excluded participants with auditory disorders in their research study but the researchers did not mention whether they excluded individuals with hearing impairments. Thus, it is not clear whether II DM type or the hearing impairment caused the delay in P300 latencies as several researchers did not control for hearing loss.

In order to measure how higher cognitive functions and central auditory pathways are affected by type II DM Kurita et al. (1996), Takeda et al. (1992) and Kurita et al. (1995) used P300 event-related potentials. The researchers found that there was a significant prolongation of the P300 latency and a decrease in the P300 amplitude when compared to the control group (Kurita et al., 1996; Kurita et al., 1995; Takeda et al., 1992). Even when individuals with type II DM show no symptoms of CNS involvement higher brain functions appear to be affected as shown by the P300 results (Kurita et al., 1996; Takeda et al., 1992).

Andreadou et al. (2012), Alvarenga et al. (2005), Chen et al. (2003), Cosway et al. (2001) and Singh et al. (2013) used the P300 specifically to determine how cognitive performance such as speed of processing of auditory information, attention and short-term memory are affected. It was found that the latency of the P300 was prolonged and the amplitude was decreased in individuals with type II DM (Andreadou et al., 2012; Chen et al., 2003; Cosway et al., 2001; Singh et al., 2013). This suggests a possibly enhanced ageing process in individuals with DM (Andreadou et al., 2012). The delay in latencies that was found in P300 testing was postulated to indicate difficulties in working memory and reduced speed of stimulus classification in individuals with type II DM (Andreadou et al., 2012).

Both Hazari et al. (2015) and Singh et al. (2013) found that individuals who have had DM for longer than five years presented with reduced amplitudes and longer latencies. As the cognitive capability of an individual decreased, the latency of P300 increased. The use of P300 event-related potentials might, therefore, be helpful in the early detection of a decline in cognition of an individual with type II DM (Hazari et al., 2015; Singh et al., 2013; Chen et al., 2003). Alvarenga et al. (2005) stated that P300 measurements of latency may be used in the early detection of changes that occur in the central auditory nervous system in individuals with DM.

Therefore, the increased P300 latencies reported in individuals with type II DM suggests changes in higher brain functions, including the hippocampus which is involved with memory and attention and might provide information regarding neurophysiological and neurobehavioral changes in individuals with DM (Kurita et al., 1996; Somani & Shukla, 2014). A decrease in the blood glucose level in diabetic patients showed an increase in latency and a decrease in amplitude of the P300 wave

which suggests dysfunction in the central auditory system (David et al., 2018). As nervous tissue is dependent on a stable glucose level, extended episodes of hypoglycaemia might lead to neurological alterations (David et al., 2018). As DM affects the brain directly improved control of DM has been associated with improvements in the cognitive functioning of diabetic individuals (Gold et al., 2007).

1.6. Rationale

Previous research showed that type II DM affects several cognitive processes including auditory processing information due to a decline in the processing resources (Koekkoek et al., 2015; Manschot et al., 2006; Messier, 2005; Sadeghi et al., 2016; Van Bussel et al., 2016). How type II DM affects the peripheral auditory nervous system is well researched. Ryan and Geckle (2000) found that there is a strong link between type II DM and cognitive dysfunction in adults older than 65 years of age.

Although there appears to be a consensus regarding the latency and amplitude of P300 in adults with type II DM, only Andreadou et al. (2012) and Singh et al. (2013) controlled for hearing loss where they excluded participants with a hearing loss, but researchers used participants above the age of 70 years. The P300 is known to be influenced by peripheral hearing loss (Reis et al., 2015; Reis & Iorio, 2007). It is not clear whether type II DM or the hearing impairment of the participants in previous studies caused the delay in P300 latencies (Cosway et al., 2001; Tandon et al., 1999).

The presence of peripheral hearing loss may, therefore, have confounded the conclusions drawn. The current research project, therefore, aimed to compare latencies and amplitude of the P300 event-related potentials in normal hearing adults with the latencies and amplitudes of participants diagnosed with type II DM

CHAPTER 2

METHODOLOGY

2.1. Aim

The main aim of the study was to compare latencies and amplitudes of the P300 event-related potentials in normal hearing adults with the latencies and amplitudes of participants diagnosed with type II Diabetes Mellitus (DM).

2.2. Research design

According to Babbie and Mouton (1998), a research design addresses the development and planning of a scientific problem in order to find something out. It comes down to making observations during the research study and then interpreting the data which you have collected (Babbie & Mouton, 1998). The research design describes what you want to observe and then, later on, analyse (Babbie & Mouton, 1998). The research study was descriptive with a cross-sectional design, from which the latencies and amplitudes of P300 event-related potentials were compared between the control group with no history of type II Diabetes Mellitus (DM), and the experimental group, all of whom were diagnosed with type II DM (Babbie & Mouton, 1998). With the use of a descriptive research design the researcher observes and then describes what they have observed, and draws conclusions (Babbie & Mouton, 1998). According to Babbie and Mouton (1998), scientific descriptions of data observed during a research study are more precise and accurate. Some phenomena can be studied through research studies that are designed in such a way that they take a cross-section of the phenomena at one time and analysing it carefully (Babbie & Mouton, 1998). The study yielded quantitative data of a numerical nature, namely numbers (amplitudes and latencies). For this research study, a non-probability purposive sampling method was used (Babbie & Mouton, 1998). P300 event-related potentials were measured of patients who had been previously diagnosed with type II DM who attend a diabetic clinic at a tertiary care hospital, as well as those at the diabetic clinic at two independently owed private practices.

2.3. Ethical considerations

When research is being conducted on human and non-human participants, it is the responsibility of the researcher to maintain a balance between the pursuit of scientific knowledge, and the rights and well-being of the participants (Gravetter & Forzano,

2012). In any form of scientific research, there are two main areas of ethical concerns namely; to ensure the welfare and dignity of the individual who participates in the research study, and to ensure that the reports written by the researcher are accurate and honest. Throughout the entire research process, the researcher needs to take ethical issues into consideration (Gravetter & Forzano, 2012). When researchers are planning their research study, they are required to take into consideration how human and animal participants will be treated throughout the course of the study, including how they will benefit from the study (Neuman, 2014). With all the steps involved in a research study, ethical issues should be taken into account and be considered. Research ethics describes all the responsibilities and obligations that a researcher has, such as to be respectful and honest to all the participants who partake in their research and who will be affected by the results of the research study (Gravetter & Forzano, 2012).

This research study has been structured according to the Declaration of Helsinki that guides doctors in biomedical research involving human participants (World Medical Association, 2013). For the research study, the researcher discussed the relevant ethical issues that were of importance to the study in the paragraphs to follow.

2.3.1. Permission from relevant authorities

Ethical approval had been obtained from the Research and Ethics Committee of the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria (protocol number 40/2018; Appendix A). Ethical approval has also been obtained at the Faculty of Humanities Research Ethics Committee at the University of Pretoria (reference number 14064066; GW20180202HS; Appendix B). Approval was also obtained from the Head of the diabetic clinic at Steve Biko Academic Hospital, Dr Frans Erasmus diabetic clinic, and Dr's Joynt, Venter, Van Rensburg and Associates diabetic clinic (Appendix C, D and E).

2.3.2. Informed consent

The researcher obtained informed consent from the research participants in English to ensure that they understood all the requirements and procedures of the research

(Gravetter & Forzano, 2012). The receptionist and/or clinic staff contacted possible participants to inquire if they would be willing to participate in the research study and whether they give the receptionist and/or clinic staff permission to go through their files and give the information to the researcher. The informed consent letter the research participants received before conducting the research can be seen in Appendix F and G. Participation in this research study was voluntary. The research participants had been informed that they could withdraw from the research study at any time (Gravetter & Forzano, 2012). When providing information to the research participants, the terminology was given in such a way that they understood the research study. The research participants were provided with verbal and written information concerning the research study.

2.3.3. Referrals

When the researcher noted that there was a possible middle ear infection or hearing loss once data collection has commenced, the researcher referred the patient to the necessary otorhinolaryngologist and/or audiologist for ear health management and possible hearing aid management (Appendix K). Participants who required further management were also given information counselling regarding the importance of consulting the necessary health care professionals concerning their otologic condition.

2.3.4. Confidentiality and anonymity

The researcher has an obligation to protect the identity and confidential information regarding the research participant. The researcher discussed the limits of confidentiality with the participant before the commencement of data collection (Gravetter & Forzano, 2012). Confidentiality but not anonymity of the research participant was ensured during the research study. The reason why anonymity was not guaranteed is that the researcher knew the identity of the participant. However, the results were kept confidential and the identity of the participant was not revealed (Babbie, 2012). For this reason, the research participants were given an identifying code to ensure anonymity of reported results and confidentiality of their identity and results.

2.3.5. Honesty

There was no form of deception used in the research study. In addition, the research participants knew precisely the nature of the research project, why the research was conducted and what had been measured. The research participants had been granted access to their test results that were explained in lay terms to the participants. Participants were given the opportunity to request access to the resulting research article. The final research study was submitted to a scientific journal for publication after peer review. In addition, to the article, the research study was presented as a Masters' dissertation, which was supervised and reviewed by Dr Leigh Biagio de Jager and Prof Paul Rheeder.

2.3.6. Plagiarism

The research study and the final written report of the research study was the original work of the researcher. All the materials used in the research report had been acknowledged and referenced accordingly using the APA 6th Addition referencing method. The research study adhered to the University of Pretoria's policy regarding plagiarism. The declaration of originality signed by the researcher can be found at the beginning of the research dissertation.

2.3.7. Data storage

The data will be stored for archiving purposes in the Department of Speech-Language Pathology and Audiology at the University of Pretoria for fifteen years (Appendix M) in digital and hard copy format in which no identifying information of the research participants are included.

2.3.8. No harm

With regard to research, the term "no harm" refers to that no participant will be harmed in any way during the research process (Babbie, 2012). The researcher took the necessary steps to ensure that the research participants were not harmed during the research study. There were no risks involved for the participants during the research

study. If the researcher became aware that the participants experienced fatigue, breaks were provided during the assessment.

2.3.9. Anticipated benefits

During the research study, the participants did not benefit directly, but the results obtained helped the researchers to describe how type II DM affects the P300 event-related potential of these participants diagnosed with type II DM. If the participants were diagnosed with a hearing loss, and they were not using any type of amplification they were referred to the Department of Speech-Language Pathology and Audiology at the University of Pretoria where further testing took place, and a suitable hearing device provided if requested.

2.3.10. Bias

P300's are an objective test measure which is therefore not influenced by the subject bias. There may have been marker bias but to prevent this, the researcher consulted other professionals to assist with the marking to ensure that the researcher was not biased in marking the waves, after which consensus had been reached. The researcher first marked the waveforms independently followed by a second experienced marker. Hereafter meetings were scheduled where the marked waves were reviewed and compared and consensus reached in the event of discrepancy. This was done for all the research participants.

2.4. Research participants

2.4.1. Study population

The study comprised of 64 participants where 32 (64 ears) had been diagnosed with type II DM, both genders (17 female, 53.13% and 14 male, 46.88%), ages from 23 – 60 years (Mean (M) 47.40 years, Standard Deviation (SD) 10.20) and 32 non-diabetic participants (64 ears) matched by age (M 47.60 years, SD 9.80) and sex. All the participants received and signed the informed consent letter to participate in the study

(Appendix F and G). Due to difficulty with finding exact age matches between the test and control group, the researcher allowed a two year age difference between the age of the test participant and their age-matched control participant. For this research study, a non-probability purposive sampling method was used (Babbie & Mouton, 1998).

2.4.2. Selection criteria

Table 1 presents the inclusion criteria as well as the rationale for the experimental participant group.

Table 1: Inclusion criteria and rationale for the experimental group

Inclusion criteria	Rationale
Participants diagnosed with type II DM	Individuals diagnosed with type II DM presented with the following diagnostic criteria: A Fasting Plasma Glucose level of 126 mg/dL (7.0 mmol/L (millimoles per litre)) or higher; or a 2 hour plasma glucose level of 200 mg/dL or higher during a 75 g Oral Glucose Tolerance Test; or a random plasma glucose of 200 mg/dL (11.1 mmol/L or higher in a patient with symptoms of hyperglycaemia (American Diabetes Association, 2010). Participants' blood glucose levels were taken on the day of testing using the Contour TS blood glucose meter to test their blood glucose. Participants were instructed to prick their fingertip with a lancet to obtain a blood sample. This drop of capillary blood was then put on a paper strip which measured blood glucose (McMillin, 1990). All the participants were taking Glucophage medication daily to control their type II DM.
Participants between the ages of 20-60 years	The average age of adults that develop type II DM is 45 years and older (National Library of Medicine, 2016). Type II DM is starting to increase in those aged 30 years and younger (Alberti et al., 2004). With greater awareness of type II DM and better identification, some participants might be of younger age and have been included in the research study.
Pure tone average (PTA)	PTA ([500Hz(frequency) + 1000Hz + 2000Hz] / 3) ranges from 0 dB to 15 dB HL (Roeser, 2013). A hearing impairment is defined as having a PTA of more than 25dB (Helleman & Dreschler, 2015). As the research study utilised adults aged 23 to 60 years they may start showing the signs of early presbycusis. This process starts to occur in adults from the age of 30-60 years (Roland, 2015). Type II DM is also associated with hearing loss with increasing age (Mishra et al., 2015). However, hearing loss increases the latency of P300 (Reis et al., 2015; Reis & Iorio, 2007). Therefore participants in the current study were required to present with a PTA of < 25 dBHL (decibel hearing level) in both ears.

Table 2 presents the inclusion criteria for the control group as well as the rationale.

Table 2: Inclusion criteria for the control group

Inclusion criteria	Rationale
Age and sex-	To accurately compare the results obtained at the end of the research study,

matched participants	adults who were age and sex-matched were used to describe the extent to which type II DM affects the temporal processing of the participants in the experimental group.
Participants with no previous history of type II DM	The participants were asked whether they had been tested before for DM and whether they had a family history of type II DM if so they were excluded from the research study. All participants underwent blood glucose testing using the Contour Plus Screening Test to test their blood glucose. Participants were instructed to prick their fingertip with a lancet to obtain a blood sample. This drop of capillary blood was then put on a paper strip which measured blood glucose (McMillin, 1990).
PTA	PTA ([500Hz + 1000Hz + 2000Hz] / 3) ranges from 0 dB to 15 dB (Roeser, 2013). As stated by Helleman and Dreschler (2015) a hearing impairment is defined as having a PTA worse than 25dB so for the research study a PTA of < 25 dBHL was considered in both ears. As the research study utilised middle-aged adults they may start showing the signs of early presbycusis which will affect their hearing. This process starts to occur in adults from the age of 30-60 years (Roland, 2015).

Presented in Table 3 is the exclusion criteria for the control and test group including the rationale behind the exclusion.

Table 3: Exclusion criteria for both groups

Exclusion Criteria	Rationale
Participants with a history of chronic alcohol abuse and/or smoke	It was found that chronic alcohol and/or smoking might worsen the mechanisms involved in the decline of the participants hearing function (Popelka et al., 2000). The P300 latency will be increased and the amplitude will be decreased in individuals with chronic alcohol and smoke abuse (Hada, Porjesz, Chorlian, Begleiter, & Polich, 2001; Polich & Ochoa, 2004).
Used medications such as sedatives and antidepressants	The use of Central Nervous System (CNS) medications appeared to cause a cognitive decline in adults (Wright et al., 2009). Numerous drugs will affect the CNS which will influence the Auditory Evoked Potential (AEP) (Biagio, 2009). If the participants were using any CNS medications this might have affected information processing and memory abilities, they were excluded from the study.
Recent infectious disease	If the participants had a previous infectious disease such as Human Immuno-deficiency Virus, Tuberculosis, meningitis, syphilis, multiple sclerosis, sepsis and encephalitis this might have influenced the results of the study due to their cognitive processes being affected. Researchers found that past infections might lead to information processing being affected and might lead to cognitive impairment (Benros et al., 2015; Chinyama, Ngoma, Menon, Hestad, & Heaton, 2016; Katan, Moon, Wright, & Elkind, 2013). Cognition was only significantly affected after 5 years of infectious disease duration (Achiron et al., 2013).
Participants having any history of psychiatric disorder	Cognitive domains such as attention, memory and executive functioning are affected by psychiatric disorders (Trivedi, 2006). It has been found that central auditory processing disorders can co-exist with psychiatric disorders (Iliadou & Iakovides, 2003). To determine whether the results obtained from P300 testing were due to type II DM or the psychiatric disorder the researcher enquired from the research participant whether they had any history of any psychiatric disorder during the pre-test interview. Participants with a history of any psychiatric disorders were therefore excluded from the study.
History of traumatic brain injury (TBI)	The most common neurocognitive consequences of TBI are memory, executive function, attention and information processing speed problems

	(Arciniegas, Held, & Wagner, 2002). This would have affected the results of P300 testing as this tests information processing speed (Arciniegas et al., 2002). It would thus not have been clear whether the results obtained would have been from type II DM or due to the brain injury.
Participants with middle ear pathology	Middle ear pathology affects the amplitude and latency of cortical auditory evoked responses (Biagio, 2009). Therefore, participants with middle ear pathology were ruled out to ensure that the results obtained were influenced by type II DM and not the middle ear pathology. Type A tympanograms with middle ear pressure between -100 daPa and +100 daPa, compliance between 0.3 ml and 1.75 ml, the volume between 1 ml to 1.4 ml with a probe tone of 226 Hz were required (Jerger, 1970). Acoustic stapedial reflex thresholds had to be present at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz (Katz, Medwetsky, Burkard, & Hood, 2009) at 70 to 90 dB which confirmed the absence of middle ear pathology (Biagio, 2009).
Cognitive impairment	Older adults are at an increased risk of having cognitive impairment (Kurlowicz & Wallace, 1999). Individuals who scored 25 or lower on the Mini-Mental State Examination (MMSE) might have had some cognitive impairment that may affect their daily living activities (Folstein, Folstein, & McHugh, 1975). There is research evidence available indicating that the speed of information processing is slower in individuals with mild cognitive impairment (Haworth et al., 2016). Thus patients who scored lower than 25 on the MMSE were ruled out because they might have a mild cognitive impairment and it would not have been clear whether the results obtained from P300 testing were due to the cognitive impairment or type II DM.

No research participants were excluded based on the exclusion criteria, after the research participants gave written consent. In addition none of the participants had diagnostic assessments prior to this research project.

2.5. Equipment and procedure for participant selection

The research study took place at the diabetic clinic of Steve Biko Academic Hospital which is a tertiary health institution, as well as at the Dr Frans Erasmus diabetic clinic and Dr's Joynt, Venter, Van Rensburg and Associates diabetic clinic which are private clinics. The participants selected for the experimental group partaking in the research study had to have been diagnosed with type II DM at the diabetic clinics. The receptionist and/or clinic staff contacted possible participants to inquire if they would be willing to participate in the research study and whether they give the receptionist and/or clinic staff permission to go through their files and give the information to the researcher. Participants selected for the experimental group were tested at the diabetic clinics from which they were selected, in a quiet room to minimize background noise. Participants selected for the control group were age and sex-matched to the experimental group and had no previous diagnosis of type II DM, where testing took place at the Department of Speech-Language Pathology and Audiology at the

University of Pretoria. Testing occurred on the same day and took approximately 90 minutes.

2.5.1. Equipment for participant selection

Table 4 describes the equipment used for participant selection

Table 4: Equipment for participant selection

Material/Equipment	Description and purpose	Appendix/ Calibration date
Informed consent form	Participants who were willing to participate in the research study completed the informed consent form and returned it to the researcher.	Appendix F (Experimental) Appendix G (Control)
Questionnaire	A questionnaire was completed to inquire information regarding the participants' age, gender, medication use, recent infectious diseases, history of psychiatric disorders, previous head injuries, noise exposure and lastly academic performance. For the control group, the only question that was additionally asked was whether they had type II DM.	Appendix H
Blood glucose test	Participants were tested on the day of testing using the Contour TS to test their blood glucose. Participants were instructed to prick their fingertip with a lancet to obtain a blood sample. This drop of capillary blood was then put on a paper strip which measured blood glucose (McMillin, 1990).	
Folstein MMSE form (Folstein et al., 1975)	Older adults are at an increased risk of having a cognitive impairment which is not considered normal (Kurlowicz & Wallace, 1999). Individuals who scored 25 or lower on the MMSE might have some cognitive impairment that may affect their daily living activities (Folstein et al., 1975). As the educational level was found to affect the MMSE scores (Crum, Anthony, & Bassett, & Folstein, 1993), participants had been required to have a minimum of 8 years of schooling. Crum et al. (1993) found that adults with this level of education presented with median MMSE scores of 26 or more. In so doing, the effect of the educational level had been accounted for. As participants were required to follow instructions given on the MMSE by eg. pointing to a pencil and wristwatch they would have had sufficient knowledge of English and literacy skills (Ridha & Rossor, 2005) if they had a minimum of 8 years of schooling even if their second language was not English. If the participants were a different language a translator was used to translate the cognitive tasks as in a study conducted by Shim, Yang, Kim, Park and Kim (2017) they used some Asian phrases that were familiar to the participants instead of using the English words (Shim et al., 2017).	Appendix J
Welch Allyn	Otoscopy was performed to observe the status of the	

otoscope	tympanic membrane and external ear canal to ensure that it was safe to perform audiological testing which required placement of probe tips and earphones in and on the ears respectively (DeRuiter & Ramachandran, 2010).	
Interacoustics AT 235 audiometer	Behavioural pure tone air thresholds calibrated in dBHL were obtained to determine the PTA ([500Hz + 1000Hz + 2000Hz] / 3) of the participants.	2018
Acoustic Immittance tympanometry (Interacoustics AT 235)	Using an 85dB SPL 226 Hz probe tone were used to perform tympanometry. Acoustic stapedial reflex thresholds had to be present at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz (Katz et al., 2009) at 70 to 90 dB (Biagio, 2009).	2018
Data capturing form	Results obtained during the assessment regarding hearing thresholds, immittance results, otoscopy and Evoked Response potentials (ERP) were written on the data capturing form.	Appendix I

2.5.2. Procedure for participant selection

Figure 2 presents the procedure followed for participant selection.

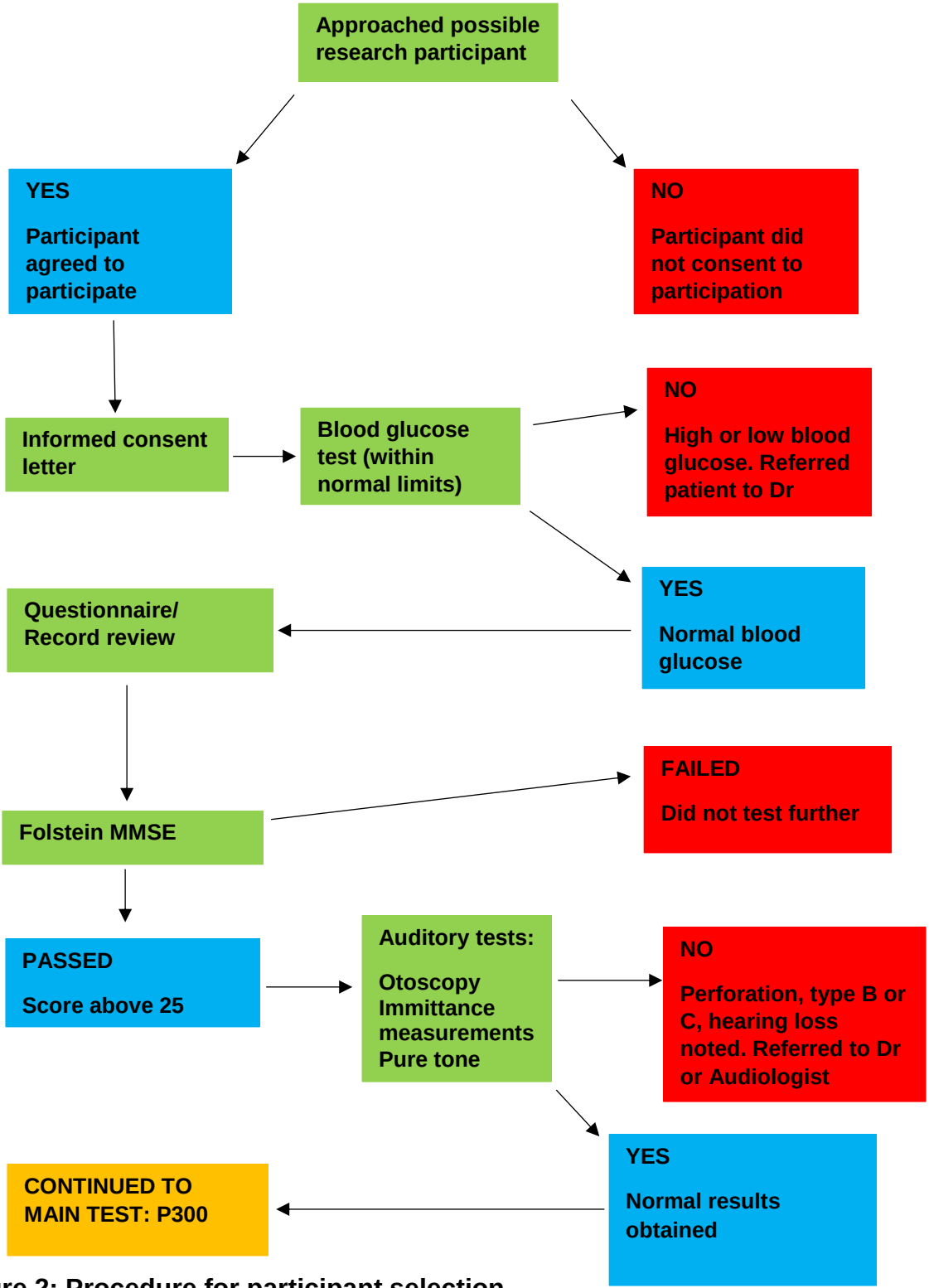

Figure 2: Procedure for participant selection

2.5.2.1. Approaching possible participants

Approval was obtained from the Head of the diabetic clinic at Steve Biko Academic Hospital, Dr Frans Erasmus diabetic clinic, and Dr's Joynt, Venter, Van Rensburg and Associates diabetic clinic (Appendix C, D and E). The receptionist and/or clinic staff contacted possible participants to inquire if they would be willing to participate in the research study and whether they give the receptionist and/or clinic staff permission to go through their files and give the information to the researcher. The researcher approached potential participants who were patients at the diabetic clinic at Steve Biko Academic Hospital, Dr Frans Erasmus diabetic clinic, and Dr's Joynt, Venter, Van Rensburg and Associates diabetic clinic, to inquire whether they wanted to participate in the research project.

2.5.2.2. Informed consent letter

When the possible research participant agreed to participate in the research study the researcher explained the reason for the study, what it would involve, and their rights as a participant of the study, should they agree. Participants were given the chance to ask questions or ask for clarification. Consenting individuals then read the participant information letter and completed the informed consent letter (Appendix F and G). Research participants were proficient in both English and Afrikaans and understood all instructions given prior to testing.

2.5.2.3. Testing blood glucose

Participants were tested on the day of testing using the Contour TS blood glucose meter to test their blood glucose. Participants were instructed to prick their fingertip with a lancet to obtain a blood sample. This drop of capillary blood was then put on a paper strip which measured blood glucose (McMillin, 1990). The mean blood glucose for was 8.23mmol/L (SD 4.20) for the diabetic group and 5.78 mmol/L (SD 1.25) for the non-diabetic group.

2.5.2.4. Questionnaire/Record review

After the participants gave written consent, a structured interview (Appendix H) took place so that the following information could be obtained:

Experimental group

1- Age in years
2- Gender
3- Usage of insulin medication (Glucophage)
4- Use of medications such as antidepressants and sedatives
5- Recent infectious diseases
6- History of psychiatric disorders
7- Previous head injuries
8- Alcohol use and/or smoking

Control group

1- Age in years
2- Gender
3- Use of medications such as antidepressants and sedatives
4- Recent infectious diseases
5- History of psychiatric disorders
6- Previous head injuries
7- Alcohol use and/or smoking
8- History of type II DM

Participants with known chronic alcohol and/or smoke abuse, medication use such as sedatives and/or antidepressants, recent infectious diseases, psychiatric disorders, traumatic brain injury, middle ear pathology and/or hearing loss, neurological involvement, and cognitive impairment which might influence the P300 results were excluded from the study.

2.5.2.5. Folstein MMSE

Older adults are at an increased risk of having a cognitive impairment (Kurlowicz & Wallace, 1999). Individuals who score 25 or lower on the MMSE may have some cognitive impairment that may affect their daily living activities (Folstein et al., 1975).

There is research evidence available indicating that the speed of information processing is slower in individuals with mild cognitive impairment (Haworth et al., 2016). Thus, patients who scored lower than 25 on the MMSE were excluded from the study as they were likely to present with a mild cognitive impairment which, may have influenced the P300 results, and would have added an additional variable. It will not have be clear whether the results obtained from P300 testing were due to the cognitive impairment or type II DM. Participants were asked to complete this form, with help from the researcher when the participants did not understand the questions and/or needed clarification. The mean Folstein MMSE was similar for both groups (diabetic: 29.69, SD 0.93; non-diabetic: 29.94 SD, 0.25).

2.5.2.6. Auditory tests

Table 5 describes all the auditory tests, their purpose, instructions given as well as the possible results obtained i.e. normal or abnormal. The auditory tests were performed to ensure that the possible research participants had normal tympanic membranes i.e. no perforation or drainage; normal middle ear functioning i.e. no middle ear infections; and that their hearing thresholds fell within the normal limits so as not to influence the P300 results. Participants presented with mean hearing thresholds for the diabetic (10.05, SD 5.34) and non-diabetic (11.72, SD 5.80) groups.

Table 5: Auditory tests for participant selection

Test	Purpose	Instructions	Normal results	Abnormal results
Otoscopy	Otoscopy was performed to determine the status of the tympanic membrane and external ear canal, to ensure that it was safe to perform audiological testing which required placement of probe tips and earphones in and on the ears respectively (DeRuiter & Ramachandran, 2010).	Participants were instructed to sit upright, head slightly bent and to remain still during the examination.	The researcher observed the following landmarks: light reflex, umbo, healthy-looking tympanic membrane and external ear canal (DeRuiter & Ramachandran, 2010). Minimal wax, not occluding the ear.	If the researcher saw that there were foreign bodies in the ear canal, evidence of ear infection, perforation or cerumen impaction (DeRuiter & Ramachandran, 2010).
Acoustic Immittance results	To determine the functioning of the middle ear and the	Participants were instructed to sit upright, and not to	Jerger (1970) Type A tympanograms:	If the results that were obtained were

	presence of a screening ipsilateral stapedial reflex at 500 - 4000 Hz at 70 to 90 dB (DeRuiter & Ramachandran, 2010).	swallow or speak during testing. Participants were told to except to hearing loud sounds and to feel a pressure build up.	with middle ear pressure between -100 daPa and +100 daPa, compliance between 0.3 ml and 1.75 ml, volume between 1.0 ml to 1.4 ml (Jerger, 1970). Acoustic reflex was required to be present at 1000 Hz at an intensity of 70 – 90 dB (Katz et al., 2009).	outside of the normal limits (Jerger, 1970). This was classified according to the following types: Type Ad, As, B and C tympanograms. No reflexes present at the frequency tested.
Pure tone audiometry	Obtained the participants hearing thresholds in order to calculate their PTA (DeRuiter & Ramachandran, 2010).	Participants were instructed to push the button every time that they heard the "beep, beep" sound, even when the sound was very soft.	If the PTA was ≤ 25 dBHL their hearing was considered normal (Helleman & Dreschler, 2015).	If the PTA was ≥ 25 dBHL their hearing was then classified as a mild, moderate, severe or profound hearing loss (Roeser, 2013).

When the individual passed all the afore-mentioned tests, they were deemed to qualify for participation in the study. Table 6 describes the equipment used for data collection.

2.6. Equipment and procedure for data collection

2.6.1. Equipment for data collection

The material and equipment used for the research study will be described in Table 6.

Table 6: Material and equipment for data collection

Material	Description and purpose	Calibration date
Eclipse (Interacoustics)	This was used to measure P300 (testing parameters given in Table 7).	January 2018
Material	**Description and purpose**	
NuPrep Skin Prep Gel	The high forehead (Fz), low forehead (Fpz), left (M_1) and right (M_2) mastoid areas were scrubbed. NuPrep skin prep	

(Weaver & Company)	gel lowers the impedances and improves the P300 tracings as well as improves the skin's conductivity.	
Ten20 Conductive Paste (Weaver & Company)	All four electrodes were placed on the areas that were scrubbed with Ten20 conductive paste. Ten20 is an adhesive paste that improves the conductivity and ensures that the electrodes remain in place during the transmittance of the electrical signals.	
Soft surgical paper tape	The soft surgical tape was used to adhere the electrodes to the skin to ensure that the electrodes did not fall off during testing.	
ER-3A insert foam eartip	Insert foam eartips were inserted into the ear canal for the transmittance of the acoustic stimuli of the P300.	

Two types of calibration that were used to calibrate the Eclipse: the ppeSPL (peak to peak equivalent Sound Pressure Level) and nHL (normal Hearing Level). The ppeSPL is the objective measure of sound stimulus pressure levels. Calibration of the transient tone burst stimuli was done using an oscilloscope and measured in dB ppeSPL. To compensate for the difference in the perceived loudness of the click and tone burst stimuli nHL was used as a correction. The brief tone burst correction value from ppeSPL to nHL as specified in ISO 389-1-2007 was then applied. For calibration of the P300, the Interacoustics Eclipse makes use of peRETSPL (reference equivalent SPL) values that are similar to the continuous pure tones, the same used in conventional audiometers (Interacoustics, 2017).

2.6.2. Procedure for data collection

Figure 3 presents the procedure followed for data collection.

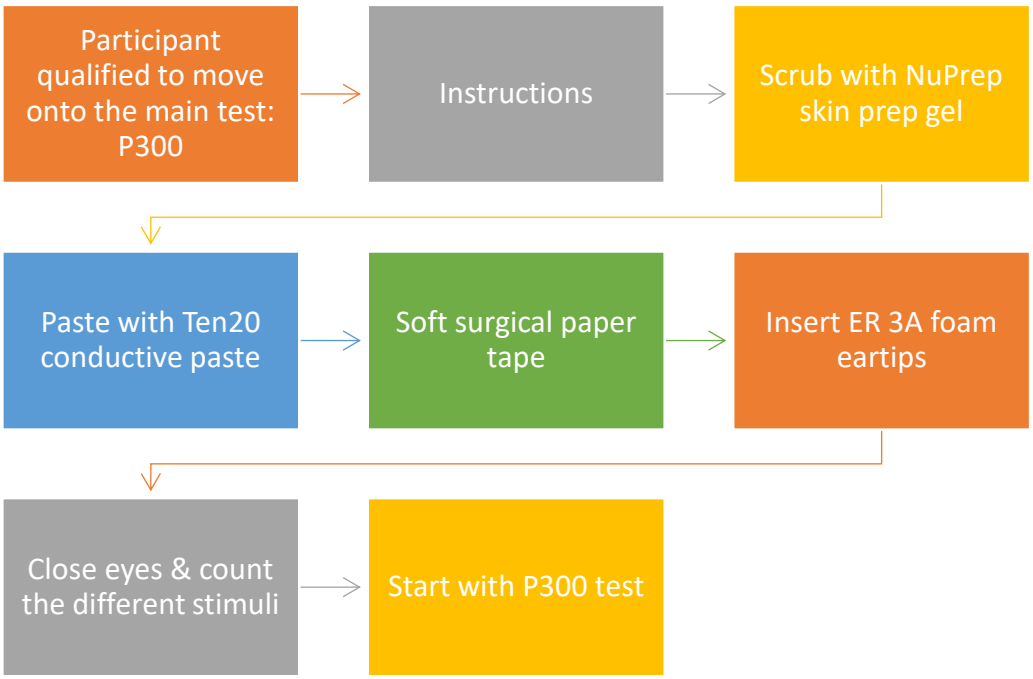

Figure 3: Procedure for data collection

In starting the electrophysiological testing, the researcher cleaned the electrode sites with prep skin scrub which ensured that the impedance was kept below 5kOhm (Mohammadkhani et al., 2013). The inverting (reference) electrodes were placed on the left (M_1) and right (M_2) mastoids and connected to the pre-amplifier. The non-inverting (active) electrode was then placed on the high forehead (Fz) and connected to the pre-amplifier. The ground electrode was placed on the low forehead (Fpz). After the electrodes were placed in position, the ER-3A earphones were inserted into both ears. Participants were in a reclining and comfortable position with eyes open but downcast to minimize eye movements (Mohammadkhani et al., 2013). Participants were instructed to recognize and keep a mental count of the rare stimulus and to ignore the frequent stimulus. Table 7 describes the electrophysiological testing, P300 parameters.

Table 7: P300 test parameters

Stimulus parameters	Suggestion	Rationale
Transducer	ER-3A	Insert earphones was more comfortable, contributes to infection control and attenuate background noise (Hall, 2007).
Stimulus type	Tone burst	2000 Hz tone bursts were used for the rare stimulus and 1000 Hz was

		used for the standard stimulus (Mohammadkhani et al.,2013).
Stimulus rate	0.6/sec	A slow rate was used, because of longer refractory time of the cortical neurons (Hall, 2007).
Oddball signal paradigm		Two different signals were used where each one generated a response. The frequent stimulus elicited a late response waveform. The infrequent stimulus was presented infrequently with a 20% probability of occurrence (Hall, 2007).
Polarity	Rarefaction	Using a signal polarity is not an important parameter for ALR (Hall, 2007).
Intensity	75 dBHL	For ALR measurements modest signal intensities are typical (Hall, 2007). Mohammadkhani et al. (2013) used 75 dBHL during P300 testing which is a supra-threshold.
Analysis time	600 ms (milliseconds)	The time domain was long enough to encompass the entire P300 wave (Hall, 2007). Analysis time of 1000 ms and pre-stimulus time of 100 ms were used.
Data points	512	
Sweeps	200	Five to seven sweeps of at least three presentations of the rare stimulus were average together per ear. The exact number of signals and traces was dependent on the resultant signal to noise ratio.
Filters	0.1 to 100 Hz	The response of the P300 consists of low-frequency energy within the EEG (Hall, 2007).
Electrodes - Type - Electrode sites I. Non-inverting (active) II. Inverting (reference electrodes)	Reusable disc electrodes	Disc electrodes were used with electrode paste to secure electrodes on the scalp (Hall, 2007). The Fz (high forehead) site for electrode placement was used (Hall, 2007). The electrode was then connected to the pre-amplifier (Mohammadkhani et al., 2013). The inverting electrode was placed on the ipsilateral mastoid bones (M_1 and M_2) and were connected to the pre-amplifier (Mohammadkhani et al., 2013).
Ground electrode	Fpz	Ground (common) electrode was placed on the low forehead (Hall, 2007).

Table 8 describes the P300 test in terms of instructions, purpose, and results.

Table 8: P300 test

Domains	Purpose	Instructions	Normal results	Abnormal results
Latency	The latency component indicates the speed of processing and the amplitude shows attentional ability (Cosway et al., 2001).	The participants were instructed to be awake and alert. They were instructed to count the number of times that they heard the odd/infrequent stimulus (Hall, 2007).	The positive peak at around the latency region around 250 to 400 ms (Hall, 2007).	Any value that falls outside the prescribed results stated by Hall (2007).
Amplitude			Around 10 to 20 µV (microvolt) (Hall, 2007).	

2.7. Reliability and validity

Validity and reliability can be defined as central concepts in measurements (Gravetter & Forzano, 2012). The term validity can be defined as the extent to which empirical measure effectively reveals the meaning of the concept being studied (Babbie & Mouton, 1998). Various methods exist to ensure the validity of a research study, for the current study the researcher had selected content and face validity. The degree to which the elements of an assessment instrument are relevant to and representative of the targeted construct of a particular assessment purpose can be seen as construct validity. Face validity, on the other hand, can be demonstrated when a measurement instrument superficially appears to measure what it claims to measure (Gravetter & Forzano, 2012). Furthermore, to ensure the internal validity of the measurements. In any quantitative research study, the internal validity can be viewed as the degree to which the researcher can say that the results they obtained are due to the experiment and not due to any other factors. The researcher ensured the internal validity of the results by ensuring that no changes occurred in the test instruments form one participant to the next. To ensure the external validity of the study the researcher provided clear descriptions of the dependant and independent variables (Maree & Van der Westhuizen, 2009).

As defined by Babbie and Mouton (1998) reliability refers to whether a specific technique or test is used and it is applied to the same object repeatedly will it give the same result and information every time. To ensure the reliability of the current research study, the researcher selected internal consistency that ensured the reliability of the measurement. Internal consistency concerns the reliability of the test components. It measures the consistency within an instrument and questions how well a set of items measures a certain characteristic or behaviour within the test (Drost, 2011). In addition, the researcher ensured that measurement procedures were stable across time, by considering stability reliability. The researcher utilised representative reliability, which relates to reliability across different groups of participants (Sarantakos, 2005).

Validity and reliability were confirmed by the following aspects during the research study (Gravetter & Forzano, 2012):

- Objective testing procedures were used.
- When the P300 waves were interpreted and marked the researcher consulted other professionals (Dr Leigh Biagio de Jager) to assist with the marking to ensure that the researcher was not biased with the marking of the waves. Consensus between the experienced markers were thus required.
- The research participants were tested under the same conditions such as a quiet room which minimized background noise.
- Five to seven sweeps of at least three presentations of the rare stimulus were average together per ear and this averaged trace was then interpreted to reduce effect of artifacts and residual noise levels.
- The same testing equipment was used on all the research participants.
- An age- and sex-matched control group was used during the research study.
- All the testing procedures were kept the same for all the research participants.
- All the instructions given to the research participants during testing were kept the same to ensure accuracy.
- All the equipment used during testing was calibrated in January 2018 prior to commencement of data collection.

2.8. Statistical analysis

Data analysis is described as the process to search for patterns within the data that was obtained during the research study (Biagio, 2009). Descriptive statistics is described as the statistical method that will be used to summarize, organize and to simplify all the results obtained from the research study (Gravetter & Forzano, 2012). For this research study, descriptive analysis was used to calculate the mean and standard deviation as well as the median and 25th and 75th percentiles of the P300 results using Stata 15 with a $p \leq 0.05$ recorded as statistically significant (StataCorp, 2017). In order to study the differences between diabetics and non-diabetics as well the effect of glucose, linear mixed model regression analyses were done when left and right ears were combined and simple linear regression when left and right ears were analysed separately. Residual analyses were done to determine the distribution of the residuals as well as to detect outliers.

CHAPTER 3

P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus

RESEARCH OUTPUT: JOURNAL ARTICLE

Note: This manuscript was edited in accordance with the editorial specifications of the Journal of American Academy of Audiology and may differ from the editorial style of the rest of the dissertation.

P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus

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3.1. Abstract

Background: P300 event-related potentials can be used to measure auditory processing speed, working memory and attention.

Purpose: The purpose of the study was to compare latencies and amplitudes of the P300 event-related potentials in normal hearing adults with the latencies and amplitudes of participants diagnosed with type II Diabetes Mellitus (DM).

Research design: A two group (with type II DM and controls) comparative study (age- and sex-matched) with a non-probability sampling method was used.

Study sample: Sixty-four participants (32 adults with diabetes, 32 adults without diabetes) between the ages of 23 to 60 years participated with a mean age of 47.50 (SD 10) years.

Data collection and analysis: Pure tone audiometry was performed to ensure participants had a pure tone average of ≤ 25 dB HL in both ears. The Folstein Mini-Mental State Examination was conducted which ensured participants had no cognitive impairment. Blood glucose levels were measured immediately prior to P300 testing. Amplitude and latency results were captured for the P300 test. Descriptive analysis was used to calculate the mean, standard deviation, as well as the median and 25^{th} and 75^{th} percentiles. In order to study the differences between adults with and without diabetes as well the effect of glucose, linear mixed model regression analyses

were performed when left and right ears were combined, and simple linear regression when left and right ears were analysed separately.

Results: For the P300 latency results, a significant statistical difference (p<0.001) was observed between the participants with diabetes (352.46 ms, SD 36.36) and participants without diabetes (314.09 ms, SD 32.08). A significant statistical difference (p<0.001) in amplitude was also observed between the participants with diabetes (12.10 μV, SD 3.70) and participants without diabetes (15.08 μV, SD 2.82). Glucose was a key moderater of amplitude but not latency after adjusting for diabetes status. Glucose had no effect on amplitude and latency for adults without type II DM.

Conclusions: It was found that normal hearing adults with type II DM on average displayed decreased P300 amplitudes ad increased latencies when compared to age and sex-matched peers without type II DM. In adults with type II DM, attention and working memory, as denoted by P300 amplitude, may deteriorate with an increase in glucose levels on the day of testing.

Keywords: type II Diabetes Mellitus, information processing speed, hippocampus, P300, amplitude, latency, glucose, attention, working memory, event-related potential

Abbreviations: DM – Diabetes Mellitus, μV – microvolt, ms – milliseconds, Hz – Hertz, M – mean, Folstein MMSE – Mini-Mental State Examination, SD – Standard Deviation, SE – Standard Error

3.2. Introduction

Interest on the impact of Diabetes Mellitus (DM) on cognitive function is increasing as the incidence of DM has increased in recent years due to an increase in longevity, urbanisation, obesity and changes in the lifestyle of the population (Andreadou et al, 2012; International

Diabetes Federation, 2017). In a recent report, it was estimated that in Africa there are 14.7 million individuals who have DM, the majority of which is diagnosed with type II DM (International Diabetes Federation, 2017).

Type II DM is caused by an inadequate compensatory insulin secretory response and a resistance to insulin action (Wrighten et al, 2008). Type II DM affects the sensory systems which damages cognitive processes such as information processing speed, general intelligence, psychomotor efficiency, learning, verbal and working memory, attention, executive function, delayed and immediate recall (Hazari et al, 2015; Hissa et al, 2002; Wrighten et al, 2008). A neurophysiological test that can be used to determine the degree to which processing speed, executive function and memory are reduced by type II DM is the P300 event-related potential (Wrighten et al, 2008). P300 is a far-field non-invasive late cortical neurophysiological technique which is based on an "oddball" paradigm during which a response is elicited when the participant attends to and detects a change in stimulus in a sequence of standard stimuli (frequent), from the other (infrequent) stimuli (Lombard, 2005; Andreadou et al, 2012). The P300 reflects information processing that is associated with memory and attention mechanisms and are dependent on internal cognitive processes (Somani and Shukla, 2014). The latency (240 - 400 ms) component indicates the speed of processing and amplitude (8 - 15 μV) demonstrates attentional ability (McPherson, 1996; Lombard, 2005). The known neural generators of the P300 are said to be the hippocampus, thalamus, inferior parietal lobe, temporal lobe, dorsolateral prefrontal cortex, cingulate cortex and amygdala (McPherson, 1996; Lombard, 2005; Somani and Shukla, 2014).

The hippocampus, in particular, is affected by type II DM, resulting in slower processing of auditory information (Sadeghi et al, 2016). This occurs due to rearrangement and changes to the electrophysiological properties of the hippocampal neurons and reductions in functional

connectivity of the hippocampus as a result of insufficient insulin availability and/or dysfunctional glucose regulation (Wrighten et al, 2008; Zhou et al, 2010). Previous studies found that P300 latencies were increased and amplitudes decreased in individuals diagnosed with type II DM (Kurita et al, 1996; Mochizuki et al, 1998; Tandon et al, 1999; Hissa et al, 2002; Chen et al, 2003; Alvarenga et al, 2005; Andreadou et al, 2012; Hamed et al, 2013; Singh et al, 2013). This increase in latencies and decrease in amplitudes indicates that type II DM results in delayed auditory temporal processing (Alvarenga et al, 2005).

It was found that individuals with a sensorineural and peripheral hearing loss presented with smaller P300 amplitudes and longer latencies yet several studies did not control for hearing loss (Reis and Iorio, 2007; Reis et al, 2015). Alvarenga et al. (2005) and Hissa et al. (2002) did perform standard audiometric testing, but the researchers still included participants in the research studies who presented with hearing loss. In the study by Hamed et al. (2013), participants did undergo standard audiometric testing but researchers did not indicate whether they excluded participants that presented with hearing loss. In addition, Tandon et al. (1999) did not indicate whether they excluded participants if they had a hearing impairment or not. In the study conducted by Kurita et al. (1996), the researchers indicated that they excluded individuals with a hearing impairment on the basis of lack of response to P300 stimuli at 70 dB. This suggests that participants with a mild to moderate loss were still included, however, the researchers did not do formal audiometric testing but ensured that stimuli were audible for P300 testing. Hazari et al. (2015) mentioned that they excluded participants with auditory disorders in their research study but did not clarify whether this included peripheral in addition central hearing disorders.

Although there appears to be a consensus that P300 is associated with increased latency and decreased amplitude in adults with type II DM, only Andreadou et al. (2012) and Singh et al.

(2013) controlled for hearing loss, but researchers used participants above the age of 70 years. The inclusion of individuals with a peripheral hearing loss may have contributed to increased P300 latency and decreased amplitudes (Reis and Iorio, 2007; Reis et al, 2015). Thus, it is not clear whether type II DM or the hearing impairment caused the increase in P300 latencies and decrease in amplitudes.

The current research project, therefore, aimed to describe P300 event-related potentials in normal hearing adults with type II DM.

3.3. Materials and methods

3.3.1. Participants

The present study was conducted at diabetic clinics at a tertiary institution including two independently owned private clinics. Ethical clearance was obtained at the Faculty of Health Sciences Research Ethics Committee (protocol no: 40/2018) as well as at the Faculty of Humanities Research Ethics Committee (reference no: 14064066; GW20180202HS).

All the participants received and signed the informed consent letter to participate in the study. Research participants were proficient in both English and Afrikaans and understood all instructions given prior to testing. Participants were required to have mean blood glucose levels and hearing thresholds and a score above 26 for the Folstein Mini-Mental State Examination (MMSE) test. Participants with known chronic alcohol and/or smoke abuse, medication use such as sedatives and/or antidepressants, recent infectious diseases, psychiatric disorders, traumatic brain injury, middle ear pathology and/or hearing loss, neurological involvement, and cognitive impairment which might influence the P300 results were excluded from the study.

The study comprised of 64 participants where 32 participants (Mean (M) 47.40, Standard Deviation (SD) 10.20) had been diagnosed with type II DM. Type II diabetic participants had a mean disease duration of 8.23 years (SD 7.50, range 2.25 to 23 years). Participants ranged from 23 to 60 years of age, (17 female, 53.13%), and 32 non-diabetic participants matched by age (M 47.60, SD 9.80) and sex.

On the day of testing, participants' blood glucose was tested by means of the Contour TS blood glucose meter Participants were instructed to prick their fingertip with a lancet to obtain a blood sample. This drop of capillary blood was then based on a paper strip which measured blood glucose (McMillin, 1990). The mean blood glucose for was 8.23mmol/L (SD 4.20) for the diabetic group and 5.78 mmol/L (SD 1.25) for the non-diabetic group.

Participants were examined using the Folstein MMSE, which is a brief 30 point neuro-psychometric test for cognitive functions which reflects memory, orientation, attention, ability to follow written and verbal commands, copying and writing (Folstein et al, 1975). Participants who obtained a score of 26 or higher (maximum = 30), were included in the study and showed no cognitive impairment, the mean score was similar for both groups (diabetic: 29.69, SD 0.93; non-diabetic: 29.94, SD 0.25).

3.3.2. Audiological assessment

Pure tone audiometry and immittance measurements were conducted using the Interacoustics AT 235 audiometer. Air conduction pure tone thresholds from 125 to 8000 Hz were conducted considering a 3-tone pure tone average of ≤ 25 dB HL, with type A tympanograms and present ipsilateral (500 to 4000 Hz) reflexes (Helleman and Dreschler, 2015) in both ears. Participants in the diabetic and non-diabetic group presented with mean pure tone averages of 10.5 dB HL (SD 5.34) and 11.72 dB HL (SD 5.80) respectively. No research participants were excluded based on the exclusion criteria, after the research participants gave written consent. The use of

pure tone average within normal limits as participant inclusion criteria did mean that some participants may have presented with elevated thresholds at 4 kHz, the mean pure tone average at 4 kHz for the control and test group were 16.56 (SD 14.36) and 16.25 (SD 15.09) respectively. However, as the rare stimuli of the P300 was set at 2000 Hz and the frequent stimuli was set at 1000 Hz the decreased hearing thresholds did not influence the P300 as these higher frequencies from 3000 to 8000 Hz were not used for P300 testing. Thus a high frequency hearing loss would not have affected the P300 amplitude and latency. Moreover, the mean pure tone average at 1 and 2 kHz was (12.58, SD 5.98; 9.30, SD 8.77) for the control group, and (9.45, SD 5.71; 10.39, SD 8.61) for the test group respectively. The inclusion and exclusion criteria were used a screening measures such as the Folstein MMSE, blood glucose and hearing test which insured the participants met the selection In addition none of the participants had diagnostic assessments prior to this research project.

3.3.3. P300 event-related potential

The Eclipse Interacoustics AEP system was used to elicit the P300 event-related potential. The AEP system was calibrated as specified in ISO 389-1-2007 before data collection commenced using ppeSPL (peak to peak equivalent Sound Pressure Level) and nHL (normal Hearing Level) (Interacoustics, 2017). Calibration was done using an oscilloscope and measured in dB ppeSPL resulting in stimuli being reported in dBnHL. Testing was performed in a quiet room, with participants in a reclining and comfortable position with eyes open but downcast to minimize eye movements. Electrode sites were cleaned using NuPrep skin prep gel and pasted with Ten20 Conductive paste to ensure impedances were kept below 5 kOhm. Two channel recording was undertaken with inverting (reference) electrode placed on the left and right mastoids, the non-inverting electrode (active) placed on Fz (high forehead), and the ground electrode was placed on the Fpz (low forehead). Stimuli were delivered through ER-3A insert

earphones. Tone burst stimuli of 1000 Hz for the frequent stimulus and 2000 Hz for the rare stimulus was used with a 20% likelihood occurrence of the infrequent target stimulus. Stimuli were presented at 75 dBnHL at 0.6/sec with a rarefaction polarity and a 0.1 to 100 Hz bandpass filter. Analysis time of 1000 ms and pre-stimulus time of 100 ms were used. Five to seven sweeps of at least three presentations of the rare stimulus were average together per ear. The exact number of signals and traces was dependent on the resultant signal to noise ratio. Participants were instructed to count the number of rare stimuli. P300 waves were marked from peak to trough (McPherson, 1996).

3.3.4. Statistical analysis

For this research study, descriptive analysis was used to calculate the mean and standard deviation as well as the median and 25th and 75th percentiles of the P300 results using Stata 15 with a $p \leq 0.05$ recorded as statistically significant (StataCorp, 2017). In order to study the differences between adults with and without diabetes as well the effect of glucose, linear mixed model regression analyses were done when left and right ears were combined and simple linear regression when left and right ears were analysed separately with independent continuous variables. Residual analyses were done to determine the distribution of the residuals as well as to detect outliers.

3.4. Results

Table 9 displays the mean and median latencies and amplitudes of participants with and without DM.

Table 9: P300 latencies and amplitudes with regard to mean, standard deviation (SD), median, interquartile range (25; 75th percentiles) (n=64)

Diabetes Mellitus (n=32)		Non-Diabetes Mellitus (n=32)	
Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)

Amplitude	12.10 (3.70)	12.12 (9.50; 14.25)	15.08 (2.82)	14.93 (13.05; 17.05)
Latency	352.46 (36.36)	348.50 (330.50; 371.50)	314.09 (32.08)	313.50 (289.00; 332.00)

n=total number of participants, IQR=interquartile range

In the mixed model analyses including random intercepts for pairs did not contribute to the model and random intercepts were only kept for individuals (as left and right ears were combined on individuals). Since pairs were not significant in the mixed model, linear regression was used for the left and right analyses. Residual analysis identified one individual for latency and two for amplitude as outliers and these were excluded from the analyses. Table 10 displays the comparison between DM vs non-DM using either linear mixed models or just linear regression. Coefficients for interaction terms are not given only the *p*-values.

Table 10: Effect of DM and glucose on amplitude and latency

	Effect of DM alone	Effect of glucose alone	Effect of DM after adjusted for glucose	Effect of glucose after adjusted for DM status
Amplitude				
Both ears				
Co-efficient	-3.26	-0.27	-3.04	-0.09
Standard Error	0.59	0.11	0.63	0.10
p-value	0.001*	0.013*	0.001*	0.342
Left ear				
Co-efficient	-3.70	-0.28	-3.51	-0.08
Standard Error	0.74	0.13	0.80	0.12
p-value	0.001*	0.036*	0.001*	0.526
Right ear				
Co-efficient	-3.15	-0.26	-2.91	-0.10
Standard Error	0.77	0.13	0.84	0.13
p-value	0.001*	0.045*	0.001*	0.448
Latency				
Both ears				
Co-efficient	34.43	0.90	37.23	-1.32
Standard Error	5.48	1.12	6.37	0.98
p-value	0.001*	0.423	0.001*	0.176
Left ear				
Co-efficient	32.81	0.50	36.93	-1.63
Standard Error	7.85	1.35	8.45	1.28
p-value	0.001*	0.711	0.001*	0.206
Right ear				
Co-efficient	36.06	1.14	38.85	-1.11
Standard Error	7.73	1.35	8.38	1.27
p-value	0.001*	0.403	0.001*	0.386

*Statistical significance

Table 9 displays that the mean amplitude was lower when compared between participants with type II DM (12.10 µV, SD 3.70) and participants without type II DM (15.08 µV, SD 2.82). Table 10 displays that there was a significant statistical effect of DM on amplitude (p<0.001). The amplitude decreased by -3.26 µV for both ears, and with -3.70 and -3.15 µV for the left and right ears respectively for the participants with diabetes compared to the participants without diabetes.

There was a statistically significant effect of glucose on amplitude (p=0.013). For every 1 mmol/L increase in glucose, the amplitude of the participants with diabetes decreased with -0.27 µV for both ears. When calculated separately for left and right ears, the difference was also statistically significant. For the left and right ears respectively there was a decrease of -0.28 (p=0.036) and -0.26 µV (p=0.045) in amplitude with every 1 mmol/L increase in glucose.

The difference between the participant groups with and without diabetes was significant on amplitude after adjusting for glucose for both ears (p<0.001), and for the left (p<0.001) and right ears (p<0.001) calculated separately. However, glucose had no significant effect on amplitude after adjusting for diabetes status for both ears (p=0.342) and left and right ears respectively (p=0.526; p=0.448).

Table 9 displays that the mean latency was higher when compared between participants with type II DM (352.46 ms, SD 36.36) and participants without type II DM (314.09 ms, SD 32.08). Table 10 displays that there was a significant statistical effect of DM on latency (p<0.001). Latency increased with 34.43 ms for both ears for the participants with diabetes compared to the participants without diabetes, and with 32.81 (p<0.001) and 36.06 ms (p<0.001) for the left and right ears respectively.

There was no statistically significant effect of glucose on latency. For every 1 mmol/L increase in glucose, latency increased by 0.90 ms for both ears (p=0.423), and when calculated separately, the latency in the left ear increased with 0.50 ms (p=0.711) and by 1.14 ms in the right ear (p=0.403).

The difference between the participant groups with and without diabetes regarding latency was also significant after adjusting for glucose for both ears (p<0.001), and for the left (p<0.001) and right ears (p<0.001) calculated separately. However, glucose had no significant effect on

latency after adjusting for diabetes status for both ears (p=0.176) and left and right ears respectively (p=0.206; p=0.386).

For combined (p=0.350; p=0.590) as well as for left (p=0.387; p=0.938) and right (p=0.891; p=0.591) ears separately, the interaction term between DM and glucose were assessed and were found not to be statistically significant for either amplitude or latency respectively.

3.5. Discussion

The current research study aimed to describe P300 event-related potentials in normal hearing adults with type II DM. The present study reported that there was a significant decrease in P300 amplitude (12.10 µV, SD 3.70) and increase in latency (352.46 ms, SD 36.36) in adults with type II DM, compared to their age and sex-matched peers without type II DM (p<0.001), which is in agreement with latencies and amplitudes reported in previous studies. Different studies conducted previously on adults with type II DM have reported latencies and amplitudes ranging from 314.8 to 405.6 ms and 8.09 to 13.96 µV respectively (Kurita et al, 1996; Mochizuki et al, 1998; Tandon et al, 1999; Hissa et al, 2002; Chen et al, 2003; Alvarenga et al, 2005; Andreadou et al, 2012; Hamed et al, 2013; Singh et al, 2013). However, the mean amplitude of the P300 in the current study was higher in comparison to the amplitude reported by Alvarenga et al. (2005; 1.98 µV) and Singh et al. (2013; 3.15 µV), and the mean latency was lower in comparison to that reported by Andreadou et al. (2012; 405.6 ms). This disparity in amplitude and latency with that of previous studies, despite similar participants, may be attributed to differences in the age of the participants. The P300 is influenced by advanced age (> 60 years) leading to an increased latency and a decrease in amplitude (Dinteren et al, 2014). The mean age of the participants in the studies by Alvarenga et al. (2005), Singh et al. (2013) and Andreadou et al. (2012) was greater than 70 years of age, which may have further increased

the latency and decreased the amplitudes reported in comparison to those of the current study, where the mean age of participants in the current study was 47.4 years.

The effect of DM was found to have a significant effect on the P300 for the total participant group. For the participant group with type II DM, amplitude was significantly lower, and latency was significantly longer than for the participants without type II DM. Glucose level on the day of testing did not influence latency of the P300. In contrast, glucose level was found to be a key moderator of amplitude. However, glucose had a significant effect on amplitude as a consequence of diabetes status. DM was found to have an effect on both amplitude and latency independently of the participant's glucose level as measured on the day of assessment. In addition, after adjusting for DM, glucose had no significant effect on P300 amplitude or latency. Previous research has not reported on the interaction of DM and glucose on the P300 in adults with or without type II DM.

DM is therefore, a significant confounding variable for both P300 amplitude and latency. Clinicians must be aware of the potential effects of DM on P300, and for those patients diagnosed with type II DM, glucose level on the day will further moderate P300 amplitude. Within the adult group with type II DM, the current study suggested that the amplitude of the P300 can be expected to decrease by 0.27 μV with every 1 mmol/L increase in glucose level. Glucose was not found to affect P300 amplitude and latency in adults without type II DM.

The reported effect of type II DM on amplitude and latency of P300 supports the assertion that cognitive functions such as working memory and attention, which are linked to amplitude of the P300 response, and auditory processing, as noted by the prolonged P300 latency, will be deleteriously affected due to the physiological changes as a result of acute hyperglycaemia (Sommerfield et al, 2004; Sadeghi et al, 2016).

No significant differences were found when comparing left and right ears for either the P300 latency or amplitude. This contradicts the late latency findings reported by both Bayazit et al. (2009) and Jerger and Martin (2004), which found that auditory stimuli was processed faster in the left hemisphere, which resulted in the so called "right-ear advantage", something that is often referred to with regard to behavioural measures of temporal auditory processing. Both studies made use of speech stimuli however, in contrast to the tone bursts used in the present study. Speech stimuli is known to be processed by Wernicke's area in the left hemisphere (Passer et al, 2009), and speech stimuli in the right hemisphere is subject to processing delay as stimuli must cross over to the left hemisphere via the corpus callosum (Jerger and Martin, 2004). The use of tonal stimuli in the present study may therefore, explain the lack of asymmetry in left and right P300 waves. Further research comparing both objective and subjective measures of temporal processing, working memory and attention in the left and right ears may corroborate the reason for the disparity of findings.

3.6. Limitations

Blood glucose levels were measured immediately prior to P300 testing. However, it must be noted that the participants were not tested at the same time of day, nor was time of testing after eating controlled for. Variation in glucose levels may therefore be attributed to these factors rather than be representative of their typical blood glucose on a given day. The duration of type II DM was not controlled for as the duration of disease in some participants was longer than others. Participants with longer duration of type II DM might have presented with prolonged P300 latencies in relation to participants with a shorter duration of disease (Hazari et al, 2015). Future researchers may want to investigate how P300 latencies and amplitudes are affected in relation to different disease duration.

3.7. Conclusions

Normal hearing adults with type II DM on average displayed decreased P300 amplitudes and increased latencies when compared to age and sex-matched peers without type II DM. Blood glucose level immediately prior to testing was found to be a significant moderator of amplitude but not latency of P300, but this was determined by diabetes status. Clinicians therefore, need to be aware that the diagnosis of type II DM is a significant confounder of accurate interpretation of P300 amplitude and latency. Moreover, for those adults with type II DM, attention and working memory, as denoted by P300 amplitude, may deteriorate with an increase in glucose levels and is susceptible to fluctuation with changes in glucose levels. The diagnosis of type II DM in adults will have a negative impact on daily listening skills, auditory temporal processing speed and attentional abilities.

CHAPTER 4

Clinical implications and conclusion

4.1. Overview

P300 event-related potentials can be used to determine the degree to which auditory processing speed, executive function and memory are reduced by type II DM (Awad et al., 2004; Wrighten et al., 2008). Previous research showed that type II DM affects several cognitive processes including auditory processing information due to a decline in the processing resources (Koekkoek et al., 2015; Manschot et al., 2006; Messier, 2005; Sadeghi et al., 2016; Van Bussel et al., 2016). How type II DM affects the peripheral auditory nervous system is well researched.

Although there appears to be a consensus regarding the latency and amplitude of P300 in adults with type II DM, only Andreadou et al. (2012) and Singh et al. (2013) controlled for hearing loss where they excluded participants with a hearing loss, but researchers used participants above the age of 70 years. The P300 is known to be influenced by peripheral hearing loss (Reis et al., 2015; Reis & Iorio, 2007). It is not clear whether type II DM or the hearing impairment of the participants in previous studies caused the delay in P300 latencies (Cosway et al., 2001; Tandon et al., 1999). The presence of peripheral hearing loss may, therefore, have confounded the conclusions drawn.

4.2. Summary of results

The current research study aimed to describe P300 event-related potentials in normal hearing adults with type II DM. The present study reported that there was a significant decrease in P300 amplitude (12.10 µV, SD 3.70) and increase in latency (352.46 ms, SD 36.36) in type II DM patients, compared to their age and sex-matched peers (p<0.001), which is in agreement with latencies and amplitudes reported in previous studies (Alvarenga et al., 2005; Andreadou et al., 2012; Chen et al., 2003; Hamed et al., 2013; Hissa et al., 2002; Kurita et al., 1996; Mochizuki et al., 1998; Singh et al., 2013; Tandon et al., 1999).

DM was found to have a significant effect on the P300 for the total participant group. For the participant group with type II DM, amplitude was significantly lower, and latency was significantly longer than for the participants without type II DM. Glucose level on the day of testing did not influence latency of the P300. In contrast, glucose

level was found to be a key moderator of amplitude. However, the effect of glucose on amplitude was found to be a consequence of diabetes status. DM was found to have an effect on both amplitude and latency independently of the participant's glucose level as measured on the day of assessment. In addition, after adjusting for DM, glucose had no significant effect on P300 amplitude or latency. Within the adult group with type II DM, the current study suggested that the amplitude of the P300 can be expected to decrease by 0.27 µV with every 1 mmol/L increase in glucose level. Glucose was not found to affect P300 amplitude and latency in adults without type II DM. No significant differences were found when comparing left and right ears for either the P300 latency or amplitude.

The reported effect of type II DM on amplitude and latency of P300 supports the assertion that cognitive functions such as working memory and attention, which are linked to amplitude of the P300 response, and auditory processing, as noted by the prolonged P300 latency, will be deleteriously affected in adults with type II DM due to the physiological changes as a result of acute hyperglycaemia (Sadeghi et al., 2016; Sommerfield, Deary, & Frier, 2004).

4.3. Clinical implications

The current research study provided objective evidence that type II DM increases the prevalence of delayed auditory information processing when the latencies and amplitudes of the P300 were compared to the latencies and amplitudes of normal hearing adults without type II DM. Audiologists should be aware of the detrimental effects when type II DM is diagnosed in their patients. Annual testing, including a complete diagnostic assessment battery and P300 testing, should be recommended to these patients to track possible changes in their information processing and cognitive function and hearing status. Audiologists should advocate the importance of blood glucose control to their patients when diagnosed with the disease. As attention and working memory, as denoted by P300 amplitude, may deteriorate with an increase in glucose levels and is susceptible to fluctuation with changes in glucose levels. Type II DM not only has an effect on processing of auditory information but also on their hearing abilities. As the presence of a hearing loss has multiple implications on the quality of life of the individual such as decreased work productivity and limited social

interactions (Hong et al., 2013). Individuals with type II DM might benefit from amplification which will improve their quality of life.

Diabetes research and care places an emphasis on the prevention and treatment of complications which results from DM (Biessels et al, 1994). The correlation found between auditory processing deficiencies and DM implies a need to monitor auditory health in DM patients (Diniz & Guida, 2009; Mochizuki et al., 1998). As DM affects the brain directly improvements in the control of diabetes has been associated with improvements in the cognitive functioning of diabetic individuals (Gold et al., 2007).

As all the participants had normal hearing, the P300 showed that there were already damage caused by type II DM even before the participants indicated that they had any difficulty with hearing and processing of sounds and auditory information. The P300 can be used clinically to obtain a baseline of information processing speed, attention and working memory in individuals diagnosed with type II DM. Annual follow-up may therefore be used to determine how fast and to what extent type II DM affect the hippocampus as the hippocampus, thalamus, inferior parietal lobe, temporal lobe, dorsolateral prefrontal cortex, cingulate cortex and amygdala, which are said to be the neural generators of the P300 (Kyizom et al., 2010; Lombard, 2005; McPherson, 1996; Schomer & Lopes da-Silva, 2011; Somani & Shukla, 2014). DM is therefore, a significant confounding variable for both P300 amplitude and latency. Clinicians must be aware of the potential effects of DM on P300, and for those patients diagnosed with type II DM, glucose level on the day will further moderate P300 amplitude.

4.4. Critical evaluation

For this research study, the strengths and limitations were critically considered. This evaluation can help in directing future research studies. The strengths and limitations of the research study will be discussed below.

4.4.1. Strengths of the study

- The research study included the individual assessment of the processing of auditory changes of a well-characterized adult population of 32 type II DM participants and 32 participants with no history of type II DM.
- The research design controlled for both age and gender with matched experimental and control group.
- The research study included a hearing test and immittance measurements to determine hearing thresholds and middle ear functioning to eliminate the presence of a peripheral hearing loss. Participants were required to have a pure tone average of ≤ 25 dB HL in both ears. This was conducted in a quiet environment to minimize the influence of background noise.
- Participants with possible middle ear pathology were excluded from the study in order to control for influence hereon on the amplitude and latency of the P300. These participants were referred for further management hereof.
- Individuals identified with hearing loss were referred for further management.
- Participants with hearing loss were not included in the study as this would have an influence on the results obtained from the P300 testing.
- Patients who scored lower than 25 on the Folstein Mini-Mental State Examination (MMSE) were excluded from the study as they were likely to present with a mild cognitive impairment which, may have influenced the P300 results, and would have added a confounding variable.
- Attention is key to accurate measurement of P300 event-related potentials (Picton, 1992). Participants were asked to indicate whenever the change in stimulus frequency was heard. This not only ensured attention was maintained during testing, but was also useful as an indication that the participant was able to follow instructions and that the change was accurately identified. Breaks were also offered during assessment if the researcher identified any participant fatigue. These measures helped in increase validity.
- Two use of objective experienced audiologists as markers of the P300 waves increased the validity of the reported data.

- Blood glucose levels were measured immediately prior to P300 testing for both participant groups. By doing this the influence of blood glucose on P300 for the experimental and the control groups could be determined.
- The study made use of mixed and linear models of regression to analyse influence of DM alone on the P300, glucose alone on the P300, the interaction of P300 latency and amplitude when DM is controlled for, and the effect of DM on latency and amplitude after adjusting for glucose. To the researcher's knowledge, this is the first time that regression models have been used to analyse P300 in adults with type II DM. The results hereof provided clear clinical implications.

4.4.2. Limitations of the study

- The degree to which blood glucose was controlled within the participant group with type II DM was not recorded in the present study. Blood glucose as measured immediately prior to testing was found to be a significant moderator of attention and working memory. However, it is not clear how P300 would be further influenced in adults with type II DM with good compared to poorly controlled glucose levels.
- Although the control group's blood glucose was tested with the screening test this might not be accurate enough to pick up possible undiagnosed type II DM. It is therefore possible that the control group may have included participants with undiagnosed type II DM.
- Blood glucose levels were measured immediately prior to P300 testing. However, it must be noted that the participants were not tested at the same time of day, nor was time of testing after eating controlled for. Variation in glucose levels may therefore be attributed to these factors rather than be representative of their typical blood glucose on a given day.
- The duration of type II DM was not controlled for in the present study as the duration of disease in some participants was longer than for others. Participants with longer duration of disease might have presented with longer latencies in relation to participants with a shorter duration of disease (Hazari et al, 2015).
- Although age and gendering 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.

4.5. Recommendation for future research

The duration of type II DM was not controlled for as the duration of disease in some participants was longer than others. Participants with longer duration of type II DM might have presented with prolonged P300 latencies in relation to participants with a shorter duration of disease (Hazari et al, 2015). Future researchers may want to investigate how P300 latencies and amplitudes are affected in relation to different disease duration. In addition, larger samples sizes of patients diagnosed with type II DM can be tested and well as more specific age categories so that normative data for P300 in adults with type II DM can be determined.

Blood glucose levels were measured immediately prior to P300 testing. However, it must be noted that the participants were not tested at the same time of day, nor was time of testing after eating controlled for. Variation in glucose levels may therefore be attributed to these factors rather than be representative of their typical blood glucose on a given day. Glucose levels prior was found to influence attention and working memory in adults with type II DM. Further behavioural testing of attention and working memory, and of the broader spectrum of auditory processing skills in this population may provide further insight into the influence of glucose in adults with type II DM. The study may also be repeated with control of the time after eating to determine if results and influence of glucose is replicated.

The current study made use of tonal stimuli and no difference between left and right ear P300 potentials waves were found. Future use of P300 event-related potentials using speech stimuli may provide further elucidation of left and right ear function in this population.

4.6. Conclusions

Individuals diagnosed with type II DM with normal hearing had statistically reduced P300 amplitudes (p<0.001) and increased latencies (p<0.001) compared to the age

and sex-matched control group with no history of type II DM. Blood glucose level immediately prior to testing was found to be a significant moderator of amplitude but not latency of P300, but this was determined by diabetes status. Clinicians therefore, need to be aware that the diagnosis of type II DM is a significant confounder of accurate interpretation of P300 amplitude and latency. Moreover, for those adults with type II DM, attention and working memory, as denoted by P300 amplitude, is subject to daily fluctuation with changes in blood glucose levels. The diagnosis of type II DM in adults will therefore have a negative impact on daily listening skills, auditory temporal processing speed and attentional abilities.

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Appendix A

Ethical application form (Heath Sciences)

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

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Faculty of Health Sciences Research Ethics Committee

1/02/2018

Approval Certificate
New Application

Ethics Reference No: 40/2018

Title: P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus

Dear Natasha van der Westhuizen

The **New Application** as supported by documents specified in your cover letter dated 24/01/2018 for your research received on the 24/01/2018, 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 (**40/2018**) 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 deepeka.behari@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

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Appendix B

Ethical approval letter (Humanities)

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

1 March 2018

Dear Ms van der Westhuizen

Project:	**P300 event related potential in normal hearing adults with type II DM**
Researcher:	**N van der Westhuizen**
Supervisors:	**Prof B Vinck and Dr L Biagio de Jager**
Department:	**Speech-Language Pathology and Pathology**
Reference number:	**14064066 (GW20180202HS)**

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

I have pleasure in informing you that the Research Ethics Committee formally **approved** the above study at an *ad hoc* 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 your actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: tracey.andrew@up.ac.za

cc: Prof B Vinck and Dr L Biagio de Jager (Supervisor)
Prof J van der Linde (Acting-HoD)

Appendix C

Request for permission to conduct research at the diabetic clinic at Steve Biko Academic Hospital, Dr Frans Erasmus and Dr's Joynt, Venter, van Rensburg and Associates

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Attention: Professor Paul Rheeder

Coordinator of the Diabetic Clinic at Steve Biko Academic Hospital

Dear Professor Rheeder,

RE: PERMISSION TO CONDUCT A RESEARCH STUDY REGARDING TEMPORAL PROCESSING OF NORMAL HEARING ADULTS WITH TYPE II DIABETES MELLITUS

I, (Natasha van der Westhuizen) am a registered student for the following programme at the Department of Speech-Language Pathology and Audiology, University of Pretoria: B Audiology (Research). I am required to write a dissertation, resulting from a research project, under the supervision of Professor Bart Vinck and Dr Leigh Biagio de Jager. Below is a summary of the proposed research.

The aim of the current research project will be to describe P300 event-related potentials in normal hearing adults with type ll DM.

The objectives of the study are:

- The main objective of the study is to describe P300 event-related potentials in normal hearing adults with type ll DM.

The target group of the study is male and female individuals between the ages of 40 to 60 years who have Type II Diabetes Mellitus at the following hospital: Steve Biko Academic Hospital. A descriptive quantitative research design will be used in this research study. The data will be obtained in a cross-sectional manner after which the results will be analysed numerically. The procedures that will be included in this

research project are otoscopy (visual inspection of the ear), immittance measures (evaluation of middle ear functioning), hearing test and P300 testing.

The otoscopy procedure is merely an inspection of the outer ear canal with an otoscope (light). An ear tip will be placed in the outer ear to measure middle ear function, which is a quick procedure where the equipment does the measurements by itself. For the hearing test, you will be requested to press a button every time you hear a “beep” sound in order to determine your hearing sensitivity. The P300 test will involve the following: In starting the electrophysiological testing, the researcher will clean three electrode sites on your head and behind your ears with prep skin scrub. After the electrodes are placed in position, earphone tips will be inserted into both ears. You will be instructed to lie down comfortably, with eyes closed in order to eliminate eye movements during testing. You will be instructed to pay attention to the odd stimulus (sound) which you will hear and count how many times that you hear that odd stimulus in a sequence of standard stimuli (sounds). The tests will all be performed in the daytime in the morning. You will only participate in the test once.

I sincerely believe that this research will be of benefit to the field of Audiology and Type II Diabetes Mellitus management and will allow for evidence-based practice which will improve the quality of the services provided.

In order to conduct this study, data on adults diagnosed with Type II Diabetes Mellitus will be captured. If permission for this is granted from you as the coordinator of the Diabetic Clinic at Steve Biko Academic Hospital, you are requested to sign this letter of consent.

Please contact us should you require more information. Thank you in advance for your time and cooperation.

Yours sincerely,

Natasha van der Westhuizen
Audiology student
natashavanderwesthuizen439@yahoo.com

078 868 9359

Dr. Leigh Biagio de Jager
Supervisor
Clinical Audiologist/Lecturer

PERMISSION FOR THE USE OF INFORMATION OF TYPE II DIABETES MELLITUS ADULTS FROM THE DIABETIC CLINIC AT STEVE BIKO ACADEMIC HOSPITAL

Herewith I, **Professor Paul Rheeder** give permission that patients with Type II Diabetes Mellitus from the Diabetic Clinic at Steve Biko Academic Hospital may be used for the research project titled: P300 event-related potentials in normal hearing adults with Type II Diabetes Mellitus.

Professor Paul Rheeder
Coordinator: Diabetic Clinic
Date: 4 January 2018

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Attention: Dr F Erasmus

Dear Dr Erasmus,

RE: PERMISSION TO CONDUCT A RESEARCH STUDY REGARDING TEMPORAL PROCESSING OF NORMAL HEARING ADULTS WITH TYPE II DIABETES MELLITUS

I, (Natasha van der Westhuizen) am a registered student for the following programme at the Department of Speech-Language Pathology and Audiology, University of Pretoria: B Audiology (Research). I am required to write a dissertation, resulting from a research project, under the supervision of Professor Bart Vinck and Dr Leigh Biagio de Jager. Below is a summary of the proposed research.

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The target group of the study is male and female individuals between the ages of 20 to 60 years who have Type II Diabetes Mellitus. A descriptive quantitative research design will be used in this research study. The data will be obtained in a cross-sectional manner after which the results will be analysed numerically. The procedures that will be included in this research project are otoscopy (visual inspection of the ear),

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In order to conduct this study, data on adults diagnosed with Type II Diabetes Mellitus will be captured. If permission for this is granted from you, you are requested to sign this letter of consent.

Please contact us should you require more information. Thank you in advance for your time and cooperation.

Yours sincerely,

Natasha van der Westhuizen
Audiology student
natashavanderwesthuizen439@yahoo.com

078 868 9359

Dr Leigh Biagio de Jager
Supervisor
Clinical Audiologist/Lecturer

PERMISSION FOR THE USE OF INFOMATION OF TYPE II DIABETES MELLITUS ADULTS

Herewith I, **Dr F Erasmus** give permission that adults with Type II Diabetes Mellitus may be used for the research project titled: P300 event related potentials in normal hearing adults with Type II Diabetes Mellitus.

Dr F Erasmus

Date: 6/3/2018

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

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Attention: Dr van Rensburg

Dear Dr. van Rensburg,

RE: PERMISSION TO CONDUCT A RESEARCH STUDY REGARDING TEMPORAL PROCESSING OF NORMAL HEARING ADULTS WITH TYPE II DIABETES MELLITUS

I, (Natasha van der Westhuizen) am a registered student for the following programme at the Department of Speech-Language Pathology and Audiology, University of Pretoria: B Audiology (Research). I am required to write a dissertation, resulting from a research project, under the supervision of Professor Bart Vinck and Dr Leigh Biagio de Jager. Below is a summary of the proposed research.

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Please contact us should you require more information. Thank you in advance for your time and cooperation.

Yours sincerely,

Natasha van der Westhuizen
Audiology student
natashavanderwesthuizen439@yahoo.com

078 868 9359

Dr Leigh Biagio de Jager
Supervisor
Clinical Audiologist/Lecturer

PERMISSION FOR THE USE OF INFORMATION OF TYPE II DIABETES MELLITUS ADULTS FROM THE DIABETIC CLINIC

Herewith I, **Dr van Rensburg** give permission that patients with Type II Diabetes Mellitus from the Diabetic Clinic may be used for the research project titled: P300 event-related potentials in normal hearing adults with Type II Diabetes Mellitus.

Dr van Rensburg

Date: 6/4/2018

Dr's Joyat, Veater & Ass.
P.O. Box 154
Witbank
1035

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Appendix D

Permission to conduct research at Steve Biko Academic Hospital

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

Attention: Dr M Kenoshi

Chief Executive Officer at Steve Biko Academic Hospital

Dear Dr Kenoshi,

RE: PERMISSION TO CONDUCT A RESEARCH STUDY REGARDING TEMPORAL PROCESSING OF NORMAL HEARING ADULTS WITH TYPE II DIABETES MELLITUS

I, (Natasha van der Westhuizen) am a registered student for the following programme at the Department of Speech-Language Pathology and Audiology, University of Pretoria: B Audiology (Research). I am required to write a dissertation, resulting from a research project, under the supervision of Professor Bart Vinck and Dr Leigh Biagio de Jager. Below is a summary of the proposed research.

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research project are otoscopy (visual inspection of the ear), immittance measures (evaluation of middle ear functioning), hearing test and P300 testing.

The otoscopy procedure is merely an inspection of the outer ear canal with an otoscope (light). An ear tip will be placed in the outer ear to measure middle ear function, which is a quick procedure where the equipment does the measurements by itself. For the hearing test, you will be requested to press a button every time you hear a “beep” sound in order to determine your hearing sensitivity. The P300 test will involve the following: In starting the electrophysiological testing, the researcher will clean three electrode sites on your head and behind your ears with prep skin scrub. After the electrodes are placed in position, earphone tips will be inserted into both ears. You will be instructed to lie down comfortably, with eyes closed in order to eliminate eye movements during testing. You will be instructed to pay attention to the odd stimulus (sound) which you will hear and count how many times that you hear that odd stimulus in a sequence of standard stimuli (sounds). The tests will all be performed in the daytime in the morning. You will only participate in the test once.

I sincerely believe that this research will be of benefit to the field of Audiology and Type II Diabetes Mellitus management and will allow for evidence-based practice which will improve the quality of the services provided.

In order to conduct this study, data on adults diagnosed with Type II Diabetes Mellitus will be captured from the Diabetic Clinic at Steve Biko Academic Hospital. If permission for this is granted from you as the Chief Executive Officer at Steve Biko Academic Hospital, you are requested to sign this letter of consent.

Please contact us should you require more information. Thank you in advance for your time and cooperation.

Yours sincerely,

Natasha van der Westhuizen
Audiology student
natashavanderwesthuizen439@yahoo.com

078 868 9359

Dr. Leigh Biagio de Jager
Supervisor
Clinical Audiologist/Lecturer

PERMISSION FOR THE USE OF INFORMATION OF TYPE II DIABETES MELLITUS ADULTS FROM THE DIABETIC CLINIC AT STEVE BIKO ACADEMIC HOSPITAL

Herewith I, **Dr M Kenoshi** give permission that adults with Type II Diabetes Mellitus from the Diabetic Clinic at Steve Biko Academic Hospital may be used for the research project titled: P300 event-related potentials in normal hearing adults with Type II Diabetes Mellitus.

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

Dr M Kenoshi
Chief Executive Officer
Date: 10 January 2018

Appendix E

Permission to access records/files from Steve Biko Academic Hospital, Dr Frans Erasmus and Dr's Joynt, Venter, van Rensburg and Associates

Permission to access Records / Files / Data base at Steve Biko .....Hospital

TO:
The [CEO] Chief Executive Officer of SBA Hospital

Re: Permission to do research at SBA Hospital

TITLE OF STUDY: P300 event related potentials in normal hearing adults with type 2 DM

This study is approved by the relevant Head of Department [HOD]: Prof C Theunissen 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 Rheeder. 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 Rheeder Signature Rheeder on behalf of student Natasha vd Westhuizen
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. SS Maraburé

Name of hospital / clinic: Steve Biko Academic Hospital

Signature: Date: 2018/01/10

GAUTENG PROVINSIALE REGERING
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

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Permission to access Records / Files at Dr Frans Erasmus Diabetic Clinic

To: Dr F Erasmus
Diabetic Clinic
29 Jan Booysen Street
Annlin
Pretoria
0182

From: Natasha van der Westhuizen
The Department of Speech-Language Pathology and Audiology

Re: Permission to do research at Dr Frans Erasmus Diabetic Clinic

Professor Bart Vinck, Dr Leigh Biagio de Jager and I are researchers working at the University of Pretoria, Department of Speech-Language Pathology and Audiology and I am requesting permission on behalf of all of us to conduct a study on type II diabetic patients, grounds that involves access to patient records.

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

The title of the study: **P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus**

The researchers request access to the following information:

Access to the clinical files, record book, and the database.

We intend to publish the findings of the study in a professional journal and/ or 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 patient a random code number.

We have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely
Natasha van der Westhuizen

BA Audiology Student (University of Pretoria)

Permission to do the research study at this clinic and to access the information as requested, is hereby approved.

Dr F Erasmus

Signature

6/3/2018.

Date

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

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

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Permission to access Records / Files at Dr's. Joynt, Venter, van Rensburg and Associates Diabetic Clinic

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

From: Natasha van der Westhuizen
The Department of Speech-Language Pathology and Audiology

Re: Permission to do research at Dr's. Joynt, Venter, van Rensburg and Associates Diabetic Clinic

Professor Bart Vinck, Dr Leigh Biagio de Jager and I are researchers working at the University of Pretoria, Department of Speech-Language Pathology and Audiology and I am requesting permission on behalf of all of us to conduct a study on type II diabetic patients, grounds that involves access to patient records.

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

The title of the study: **P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus**

The researchers request access to the following information:

Access to the clinical files, record book, and the database.

We intend to publish the findings of the study in a professional journal and/ or 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 patient a random code number.

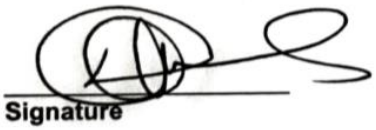
We have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely
Natasha van der Westhuizen

BA Audiology Student (University of Pretoria)

Permission to do the research study at this clinic and to access the information as requested, is hereby approved.

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



Signature

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

Hospital Official Stamp

Appendix F

Informed consent letter for experimental group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

INFORMATION LEAFLET AND INFORMED CONSENT FOR TYPE 2 DIABETES MELLITUS PARTICIPANTS

P300 event related potentials in 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 Natasha van der Westhuizen at 078 868 9359. 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 the study is to describe P300 event-related potentials in normal hearing adults with type II DM. An age and sex-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

The research will take place at the Department of Speech-Language Pathology and Audiology at the University of Pretoria and/or Steve Biko Academic Hospital or Dr F Erasmus Diabetic Clinic. Before any testing takes place your file will be examined by the researcher after ethical clearance and permission to peruse your file has been obtained from which the researcher will determine whether you are a possible participant based on your medical history. The procedures that will be included in this research project are a case history, blood glucose testing using the Contour TS screening test, Mini-Mental State Examination test, otoscopy (visual inspection of the ear), immittance measures (evaluation of middle ear functioning), hearing test and P300 testing. Testing will approximately be 90 minutes. If the researcher notes that there are a possible middle ear infection or hearing loss the researcher will refer you to the necessary medical Doctor and/or Audiologist for further management.

The otoscopy procedure is merely an inspection of the outer ear canal with an otoscope (light). An ear tip will be placed in the outer ear to measure middle ear function, which is a quick procedure where the equipment does the measurements by itself. For the hearing test, you will be requested to press a button every time you hear a “beep” sound in order to determine your hearing sensitivity. The P300 test will involve the following: In starting the electrophysiological testing, the researcher will clean three electrode sites on your head and behind your ears with prep skin scrub. After the electrodes are placed in position, earphone tips will be inserted into both ears. You will be instructed to lie down comfortably, with eyes closed in order to eliminate eye movements during testing. You will be instructed to pay attention to the odd stimulus (sound) which you will hear and count how many times that you hear that odd stimulus in a sequence of standard stimuli (sounds). The tests will all be performed in the daytime in the morning. You will only participate in the test once.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If the researcher notes that there is a possible middle ear infection or hearing loss the researcher will refer the patient to

the necessary medical Doctor and/or Audiologist from possible hearing aid management.

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.

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Humanities and 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 Natasha van der Westhuizen. If you have any questions about the study feel free to contact me at 078 868 9359 or at natashavanderwesthuizen439@yahoo.com. Alternatively, you can contact my supervisors, Dr Leigh Biagio de Jager at leigh.biagio@up.ac.za or Prof Bart Vinck at bart.vinck@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 AND ANONYMITY

Personal information and the results of the tests 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 anonymously used in an article.

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	Date
.....	.....
Participant signature	Date
.....	.....
Investigator's name	Date
.....	.....
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 understands 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 G

Informed consent letter for control group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

INFORMATION LEAFLET AND INFORMED CONSENT FOR PARTICIPANTS WITHOUT TYPE 2 DIABETES MELLITUS

P300 event related potentials in 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 Natasha van der Westhuizen at 078 868 9359. 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 the study is to describe P300 event-related potentials in normal hearing adults with type II DM. An age and sex-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

The research will take place at the Department of Speech-Language Pathology and Audiology at the University of Pretoria. The procedures that will be included in this research project are a case history, blood glucose testing using the Contour TS screening test, Mini-Mental State Examination test, otoscopy (visual inspection of the ear), immittance measures (evaluation of middle ear functioning), hearing test and P300 testing. Testing will approximately be 90 minutes. If the researcher notes that there are a possible middle ear infection or hearing loss the researcher will refer you to the necessary medical Doctor and/or Audiologist for further management.

The otoscopy procedure is merely an inspection of the outer ear canal with an otoscope (light). An ear tip will be placed in the outer ear to measure middle ear function, which is a quick procedure where the equipment does the measurements by itself. For the hearing test, you will be requested to press a button every time you hear a “beep” sound in order to determine your hearing sensitivity. The P300 test will involve the following: In starting the electrophysiological testing, the researcher will clean three electrode sites on your head and behind your ears with prep skin scrub. After the electrodes are placed in position, earphone tips will be inserted into both ears. You will be instructed to lie down comfortably, with eyes closed in order to eliminate eye movements during testing. You will be instructed to pay attention to the odd stimulus (sound) which you will hear and count how many times that you hear that odd stimulus in a sequence of standard stimuli (sounds). The tests will all be performed in the daytime in the morning. You will only participate in the test once.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If the researcher notes that there is a possible middle ear infection or hearing loss the researcher will refer the patient to

the necessary medical Doctor and/or Audiologist from possible hearing aid management.

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.

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Humanities and 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 Natasha van der Westhuizen. If you have any questions about the study feel free to contact me at 078 868 9359 or at natashavanderwesthuizen439@yahoo.com. Alternatively, you can contact my supervisors, Dr Leigh Biagio de Jager at leigh.biagio@up.ac.za or Prof Bart Vinck at bart.vinck@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 AND ANONYMITY

Personal information and the results of the tests 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 anonymously used in an article.

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	Date
.....	.....
Participant signature	Date
.....	.....
Investigator's name	Date
.....	.....
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 understands 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 H

Interview form for both the experimental and control group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Interview sheet for type II DM participants and for participants without type II DM

Date of testing:

_____

Randomized participant number:

_____

Cell phone number:

_____

Age:

_____

Gender:

_____

Duration of type II DM (when where you diagnosed):

_____

Medication used for type II DM (how long):

_____

_____

Other medications used (how long):

_____

_____

Any other diseases/disorders (such as recent infectious dieseases, depression, anxiety or any other psychiatric disorders; how long):

_____

Do you smoke or use alchol:

If yes how many time a day do you smoke?

If yes how many times and when do you drink alcohol?

_____

_____

Have you had a previous head injuries: (when and how did it occur?)

_____

Appendix I

Data capturing sheet for both the experimental and control group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Data capturing sheet for type II DM participants and for participants without type II DM

1. Otoscopy

Right ear: _____

Left ear: _____

2. Acoustic Immittance Measurements

Right ear:

- Tympanogram type: _____
- Ear canal pressure: _____
- Static compliance: _____
- Ear canal volume: _____

Left ear:

- Tympanogram type: _____
- Ear canal pressure: _____
- Static compliance: _____
- Ear canal volume: _____

Acoustic Reflex Measurements

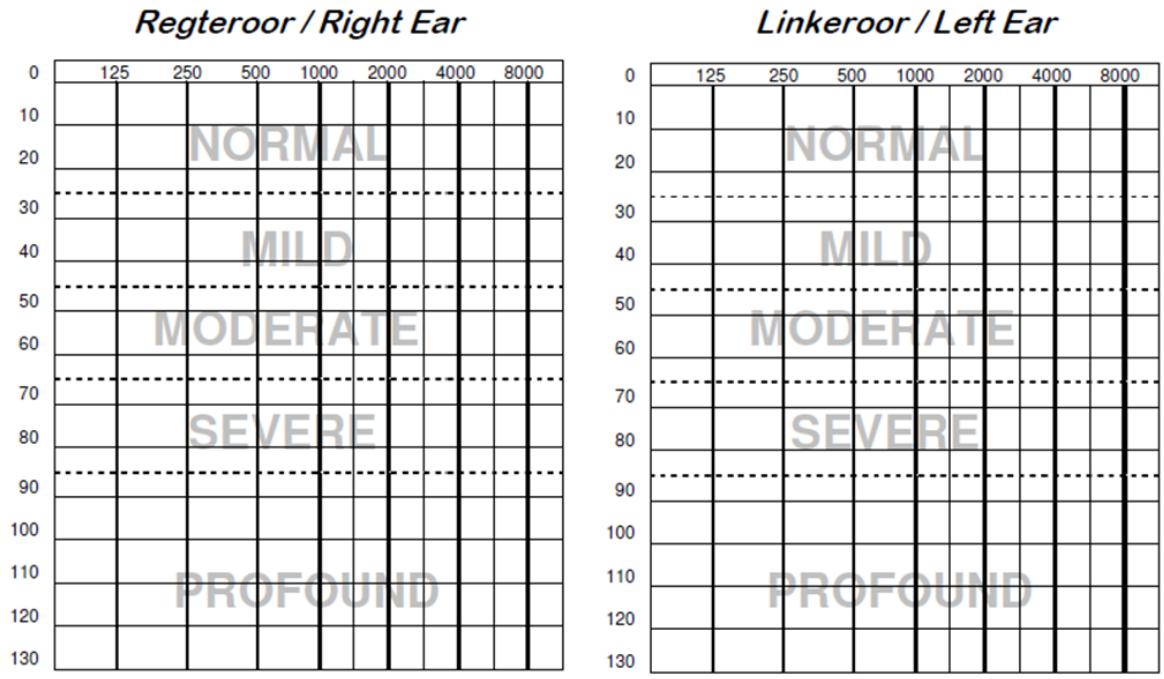
Right ear:

- 500 Hz: _____
- 1000 Hz: _____
- 2000 Hz: _____
- 4000 Hz: _____

Left ear:

- 500 Hz: _____
- 1000 Hz: _____
- 2000 Hz: _____
- 4000 Hz: _____

3. Pure Tone Audiometry



4. Electrophysiological testing (P300)

Right ear:

- Latency: _____
- Amplitude: _____

Left ear:

- Latency: _____
- Amplitude: _____

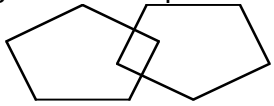
Appendix J

Mini-Mental Examination State test form for both the control and experimental group

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date:

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backward." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cut-off	<24	Abnormal
Range	<21 >25	Increased odds of dementia Decreased odds of dementia
Education	21 <23 <24	Abnormal for 8th-grade education Abnormal for high school education Abnormal for a college education
Severity	24-30 18-23 0-17	No cognitive impairment Mild cognitive impairment Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support, and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.

Appendix K

Referral letter for both the experimental and control group

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

January 2018

Dear Participant,

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

The study you participated in:

□ **P300 event related potentials in normal hearing adults with Type 2 Diabetes Mellitus**

EXPLANATION OF PROCEDURES FOLLOWED AND YOUR RESULTS

You underwent multiple assessments each contributing to the data collection for my study. Your results will be used in the research study and are attached to this letter.

Your results indicate:

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

□ P300 event-related changes indicated by one or more of the assessments done and follow up audiological intervention is recommended

Should any of the following be indicated as **F/U** by the researcher please follow up with the medical professional mentioned below:

F/U /None	**Audiological difficulty**	**Medical professional to follow up with**	**Notes**

□F/U □None	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 is currently a patient there	
□F/U □None	Abnormal Acoustic Immitance measures and/or Screening reflexes	General practitioner (clinic)	
□F/U □None	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) or Steve Biko Academic hospital (012 354 4293)	
□F/U □None	Abnormal P300 results (problems with temporal processing skills)	Speech-Language Therapist- at the Department of Speech-Language Pathology and Audiology at the University of Pretoria (012 420 2357) or Steve Biko Academic hospital (012 354 4293)	

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. Natasha van der Westhuizen. If you have any questions about the study feel free to contact me at natashavanderwesthuizen439@yahoo.com. Alternatively, you can contact my supervisor Dr. L Biagio de Jager at leigh.biagio@up.ac.za.

_____ _____

Researcher's signature Date

Natasha van der Westhuizen

Appendix L

Biostatistician letter

LETTER OF CLEARANCE FOR STATISTICS

P 300 event related potentials in normal hearing adults with type 2 Diabetes Mellitus.

Natasha van der Westhuizen
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

- The study is exploratory and no formal power or sample size calculation was done. An experimental and control group of 2 individuals is deemed feasible.

Name _____**Prof P Rheeder**_____

Signature _____ _____

Date _____**5 January 2018**_____

Appendix M

Declaration for the storage of research data and documents

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

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

I, the Principal Investigator, Natasha van der Westhuizen, of the following trial/study titled **P300 event related potentials in 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 Lynwood Road and Roper Street
Hatfield
Pretoria
South Africa

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

START DATE OF TRIAL/STUDY: 1/02/2018 END DATE OF TRIAL/STUDY: 30/09/2018

SPECIFIC PERIOD OF DATA STORAGE AMOUNTING TO NO LESS THAN 15 YEARS:

February 2018 until February 2033

[Please specify specific dates e.g. Jan 2016 - Feb 2031]

Name: Natasha van der Westhuizen

Signature: 

Date: 1 December 2017