Brainstem encoding of speech and behavioural temporal measures in individuals with Diabetes Mellitus

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13AUD001

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Dedication

I dedicate this dissertation to

Amma

My late grandmother

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The list of personals contributed to this research work is too long and I wish I could mention you all….However, Space limit and my poor memory restricts it and I will name everyone within my possibility…A big thank to those who I missed from the depth of my heart..

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Certificate

This is certify that this dissertation entitled **"Brainstem encoding of speech and behavioural temporal measures in individuals with Diabetes Mellitus"** is the bonafide work submitted as part fulfillment for the Degree of Master of Science in Audiology of the student with Registration No. 13AUD001. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other diploma or degree.

Mysuru, May, 2015

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Certificate

This is to certify that this dissertation entitled **"Brainstem encoding of speech and behavioural temporal measures in individuals with Diabetes Mellitus"** has been prepared under my supervision and guidance. It is also certified that this has not been submitted earlier to any other Universities for the award of any other Diploma or Degree.

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Declaration

This dissertation entitle **"Brainstem encoding of speech and behavioural temporal measures in individuals with Diabetes Mellitus"** is the result of my own study under the guidance of Dr. Prawin Kumar, Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, and has not been submitted earlier in any other University for the award of any Diploma or Degree.

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Abstract

The present study investigated the brainstem representation of speech along with auditory temporal processing in individuals with diabetes mellitus type 2. Diabetes mellitus is a common glucose level dependent metabolic disorder and studies have shown that hearing impairment is one among its subclinical complication. Studies to investigate auditory system involvement in diabetes is majorly focused on auditory brainstem response (ABR), otoacoustic emission and basic audiological measures. In addition to click ABR, the current study used speech evoked ABR as a tool to see the effect of diabetes on both transient and sustained response of the auditory brainstem to a consonant-vowel (CV) stimuli /da/. Along with speech evoked ABR, the temporal processing abilities assessed behaviourally using gap detection threshold (GDT) and temporal modulation transfer function (TMTF). This study was done on 35 individuals in the age range of 40 to 60 years and among this 15 individuals were having diabetes mellitus type 2 for a period of minimum five years. The study included diabetic individuals with normal hearing (n=10) as well as hearing impairment (n=5). The control population comprised of 20 non-diabetic individuals with normal hearing sensitivity (n=10) and hearing impairment (n=10). The findings suggests that individuals with diabetes have deficiency in auditory processing at the brainstem level. The latencies of Wave D & E along with amplitude of F_0 component of the speech evoked ABR were found to be affected in diabetic individual. In behavioural measures, GDT and modulation detection threshold at higher modulation frequencies were found to be affected in diabetic individuals. However caution is guaranteed to validate these findings in a large clinical population.

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Chapter 1

Introduction

"Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels" (American Diabetes Association, 2014). Ramachandran et al., 2010 has been reported that 50.8 million people are suffering from Diabetes in India whereas it has been estimated to be reaching 87 million by 2030. The prevalence of diabetic adults in southern states of India is about 20% and 10% in urban and rural populations respectively (Ramachandran & Snehalatha, 2009). Approximately 90-95% are diabetes mellitus type 2 or adult onset diabetes mellitus (American Diabetes Association, 2014).

There are well established subclinical complications of diabetes including retinopathy, nephropathy and peripheral neuropathy. The link between diabetes and hearing loss has also been investigated widely (Kakarlapudi, Sawyer, & Staecker, 2003; Lisowska, Namysłowski, Morawski, & Strojek, 2001; Vaughan, James, McDermott, Griest, & Fausti, 2006; Vesperini et al., 2011).

The earliest discussion of diabetes and hearing loss is credited to the work of Jordao in 1857 (Kakarlapudi et al., 2003; Vesperini et al., 2011). In spite of the wide literature that has been devoted for this topic, the association between diabetes and hearing loss is yet to be established clearly. However, majority of the authors claim that diabetes causes hearing loss (Kurien, Thomas, & Bhanu, 1989; Panchu, 2008; Rajendran,

Mythili, & Rao, 2011; Vaughan et al., 2006). Most of the studies to investigate the relationship between diabetes and hearing loss have been focused on the auditory brainstem response (ABR) (Lisowska et al., 2001; Vaughan et al., 2006). Various studies have reported increased absolute and inter-peak latencies of the click evoked auditory evoked responses. The inter-peak latencies I-III, III-V, I-V have been significantly found to be delayed (Baweja et al., 2013; Donald et al., 1981; Gupta et al., 2013; Huang, Lu, Chang, Tsai, & Chang, 2010; Konrad-Martin et al., 2010; Mahallik, Sahu, & Mishra, 2015) . However, studies on auditory brainsem responses mostly rely on simple stimulus like click as stimulus which is poor estimation of behaviorally relevant complex sounds such as speech (Skoe & Kraus, 2010). In addition to click, ABR can be also evoked by a wide variety of stimuli, including speech stimuli. Researchers have assessed the brainstem encoding of speech stimuli by utilizing speech evoked auditory brainstem response (ABR). Majority of the investigations recorded Speech evoked ABR using synthetic /da/ syllable of 40 ms duration (Hornickel & Kraus, 2011; Johnson, Nicol, & Kraus, 2005; Kumar & Singh, 2015; Russo, Nicol, Musacchia, & Kraus, 2004; Song, Nicol, & Kraus, 2011). The /da/ stimulus has been phenomenal in assessing both transient and periodic responses of the neural encoding. The speech evoked ABR specifically correlates to the neural encoding of speech stimuli at the brainstem level (Song, Banai, Russo, & Kraus, 2006). A speech stimulus is complex and it contains less high frequency information as compared to the click stimulus hence it needs a different acoustic processing at the brainstem level. The speech evoked ABR is an important tool to evaluate the brainstem's ability to encode the temporal aspects. Any delay in the temporal

processing will reflect in the speech evoked ABR (Parbery-Clark, Anderson, Hittner & Kraus, 2012)

The utility of speech evoked ABR in assessing the brainstem encoding of speech stimulus in diabetes mellitus is also been investigated recently. This preliminary study found significant abnormalities in the transient as well as sustained measures of speech evoked ABR (Gupta, Bhat & Kumar, 2015). Altered encoding of speech at the brainstem level as shown through speech evoked ABR also gives a possible research direction to validate these findings by correlating to behavioural temporal measures. Apart from objective way of measuring time locked responses, similar findings can be obtained using behavioural measures too.

The perception of sound or of the alteration of sound within a restricted or defined time domain can be referred as temporal processing (Shinn & Musiek, 2003). The common way to measure temporal processing by psychoacoustic measures is gap detection threshold (GDT) and temporal modulation transfer function (TMTF). The gap detection assess the individual's ability to detect the presence of a temporal gap in the stimulus and it reflect the temporal acuity of the individual. In a similar line, TMTF measures the individual's threshold to detect sinusoidal amplitude modulation to different modulation rates (Shen & Richards, 2013). As it has long been known that diabetes is associated with hearing loss, it is also important to investigate the changes in temporal processing in these individuals independent of hearing loss. The current study will be using both TMTF and GDT as psychoacoustic tools to measure temporal processing.

Temporal processing abilities are important in speech perception. Evidence clearly indicates that there is deterioration in such abilities with chronological aging (Strouse, Ashmead, Ohde, & Grantham, 1998). Auditory temporal processing have been significantly found to be affected in non-diabetic individuals with hypoglycaemia (McCrimmon, Deary & Frier, 1997). However, the temporal acuity in diabetic individuals has not been explored much using psychoacoustic measures. As diabetes is a systemic illness, the higher auditory structures can be vulnerable with this disease and it can affect the temporal processing abilities.

1.1. Need for the study

Studies to investigate auditory system involvement in diabetes mellitus majorly focused on either click evoked ABR or basic audiological evaluations including pure-tone audiometry and otoacoustic emission screening (Kakarlapudi et al., 2003; Konrad-Martin et al., 2010; Lisowska et al., 2001; Vaughan et al., 2006; Vesperini et al., 2011). However, except the recent study by Gupta et al. (2015), there is dearth of literature regarding the speech sound processing at the brainstem level in individuals with diabetes mellitus. This suggests the importance of an investigation to focus the speech sound encoding at the brainstem level in such individuals.

Human brainstem structures are key in encoding the auditory temporal information. Evoked potentials and nerve conduction studies have clearly shown the involvement of central and peripheral neuropathy in diabetes mellitus (Dolu et al., 2003). However the integrity of auditory brainstem structure in diabetes is not yet investigated using psychoacoustic measures such as TMTF and GDT. Hence present study focuses on

psychoacoustic measures in addition to brainstem encoding of speech in individuals with Diabetes mellitus type 2.

1.2. Aim of the study

The present study aimed to investigate the brainstem encoding of speech by electrophysiological testing as well as the temporal processing abilities by means of psychoacoustic measures in individuals with diabetes mellitus.

1.3. Objectives of the study

The following objectives were be taken to achieve the above mentioned aims.

1. To find out the latency of the onset, sustained and offset components of the speech evoked ABR inindividuals with diabetes mellitus type 2.
2. To find out the amplitude of fundamental frequency (F_0) and its higher formants (F_1 & F_2) of the sustained portion speech evoked ABR in individuals with diabetes mellitus type 2.
3. To correlate absolute and interpeak latencies of click evoked ABR with latency measures of speech evoked ABR in individuals with diabetes mellitus type 2.
4. To explore the temporal processing abilities in diabetic individuals through behavioural measures such as GDT and TMTF.

Chapter 2

Literature Review

2.1. Diabetes and hearing impairment

Jordao (1857) was the first one to associate diabetes with hearing loss. Following this case report with diabetes and hearing loss, the incidence of high frequency hearing loss in diabetic individuals has been further reported by Edger in 1915 (as cited in Kakarlapudi et al., 2003). Inspite of the variability in findings majority of the studies suggests that diabetes is associated with higher incidence or progression of sensorineural hearing loss (Cullen & Cinnamond, 1993; Kakarlapudi et al., 2003; Kurien et al., 1989; Lisowska et al., 2001; Panchu, 2008; Vaughan et al., 2006; Vesperini et al., 2011).

A meta-analysis by Akinpelu, Mujica-Mota and Daniel (2014) on the available evidence of relationship between diabetes and hearing impairment shows significant correlation. This study included systematic review of 18 articles. Findings of this review article suggests that diabetic individuals had higher mean pure- tone average (PTA) than non-diabetic individuals. Majority of the studies included in this review article reveals that diabetic individuals have at least mild hearing loss compared to age matched controls. Also age and duration of diabetes play a significant role in the occurrence of hearing loss.

Kakarlapudi et al. (2003) investigated the effect of sensorineural hearing loss on diabetes. Higher incidence of hearing loss was found in diabetic individuals compared to age matched non diabetic individuals. In this retrospective data review, the prevalence of

sensorineural hearing loss in diabetic individuals were 13.1 % compared to non-diabetic group (10.3%).

In one of the recent study, Vesperini et al. (2011) performed detail audiological evaluation in individuals with diabetes mellitus type 2. The study showed that individuals with diabetes mellitus type 2 were having increased hearing thresholds at frequencies above 4 kHz. Otoacoustic emission (OAE) suggested decreased amplitude of TEOAE and DPOAE in individuals with diabetes mellitus type 2. The auditory brainstem responses (ABR) also showed abnormal neural responses. This study recommended a combined battery of tests including cochlear and neural assessment to screen and monitor hearing impairment in diabetes.

Few Indian studies have also explored the higher incidence of hearing loss in individuals with diabetes (Kurien et al., 1989; Panchu, 2008; Rajendran et al., 2011). Kurien et al. (1989) investigated on pure-tone thresholds in individuals with diabetes mellitus. Among the 30 diabetic patients and 30 healthy controls studied, it was found that diabetics had a poorer hearing threshold than the non-diabetic subjects irrespective of age. Diabetics with poorly controlled glycemic level and complicated diabetics had significant, high frequency hearing loss as compared to those who were well controlled and uncomplicated. Though all individuals had diabetes more than three years, there was no relationship between duration of the diabetes and the level of hearing loss.

A study by Panchu (2008) also found significant correlation between auditory acuity and diabetes mellitus type II. Among the 42 diabetic individuals and 41 healthy controls included in the study, the former group had higher hearing thresholds in all the

frequencies suggestive of sensorineural hearing loss. This investigation also suggested that individuals with poor glucose control (HbA1C > 8%) had poor hearing thresholds than those who have controlled glucose level.

Rajendran et al. (2010) also investigated incidence of hearing loss in individuals with diabetes mellitus type 2 in Indian population. This study revealed that diabetic individuals had significantly high incidence of sensorineural hearing loss (73.3%) compared to non-diabetic individuals (6.7%). The characteristics of hearing loss were bilateral, mild-to-moderate, and predominantly at higher frequencies. However, it was evident in the study that, duration of the diabetes and HbA1C level had no significant effect on hearing loss.

Thus, from the various investigations seen above it can be conclude that diabetes mellitus is associated with reduced hearing thresholds, at least in the higher frequencies. Also it is evident that poorly controlled diabetes have more effect on hearing acuity than controlled diabetes (Kurien et al., 1989; Panchu, 2008). However duration of diabetes have less effect on hearing acuity (Panchu, 2008; Rajendran et al., 2011). Along with investigations on peripheral hearing loss in diabetes, researchers have also focused on higher auditory potentials.

2.2. Auditory Brainstem Response (ABR) in diabetics

To begin with the earliest literature evidence on ABR investigation in diabetes, Donald et al. (1981) in his investigation on 20 insulin treated diabetic individuals, found altered ABR responses. Absolute latencies of wave I and II were appeared to be normal, suggestive of unaffected 8th nerve transmission time. However, absolute latencies of

wave III and V along with interpeak latencies of I- III and I-III were prolonged and indicating involvement of brainstem to midbrain lesion. The study also revealed no significant relationship between ABR responses with blood glucose level and duration of diabetes.

Among the various subsequent investigations, majority of the studies suggested that there is impaired auditory brainstem responses in diabetic individuals (Baweja et al., 2013; Gupta et al., 2013; Konrad-Martin et al., 2010; Mahallik et al., 2014; Talebi, Moosavi, Mohamadzade & Roshandel, 2008). Konrad-Martin et al. (2010) studied the effect of diabetic severity on ABR. This cross sectional study had a large sample 166 diabetic individuals and 163 non diabetic individuals. All the individuals had not more than moderate hearing losses. Results of the study suggested abnormal wave V latency, I-V interval, and reduced wave V amplitude in subjects with insulin dependent diabetes mellitus under 50 years. Though duration of diabetes was not associated with ABR responses, HbA1C significantly associated with wave V latency and amplitude as well as I-V interpeak latency.

Talebi et al. (2010), in a case controlled study included 50 diabetic individuals and 69 non-diabetic controls. The findings of the study revealed significant abnormalities in the latency measures of ABR. The subjects in the diabetic group had altered responses including the latency of waves IV, V, and an IPL of III-V in the right side and latency of wave III, V and an IPL of III-V in left side. This study also suggested that the earlier peaks I and II are less affected than the later peaks III, IV and V. However, there was no significant relationship between fasting blood sugar level (FBS) and latencies of click

ABR observed in the group. Also, there was also no relationship between HbA1C and ABR latencies noticed.

In an investigation, Baweja et al. (2013) observed the abnormal ABR responses in middle aged females. The study included 116 female diabetics and 100 age matched controls. Among the various latency measures analysed, only the mean latencies of wave V and interpeak latency of I-V were found to be statistically significant. Interpeak latency of I-III was also found to be statistically significant, but only in right ear. The latencies of the earlier peaks I and II were found to be not significantly different in both the ears. This may also suggests that inspite of higher brainstem dysfunction, the 8th nerve abnormality is less in individuals with diabetes mellitus.

Gupta et al. (2013) also found significant alteration in the ABR responses in diabetic males. This cross sectional study included 125 diabetic individuals and 126 age matched non-diabetic controls. The latencies of wave III and V was significantly delayed in diabetic individuals bilaterally. However latencies of wave IV was only statistically significant in right ear. Along with absolute latencies, interpeak latencies of III-V and I-V were also significantly prolonged in diabetic males than non-diabetic males bilaterally. There was also a strong positive correlation between ABR latencies and fasting blood glucose level, but it was statistically not significant. Correlation with duration of diabetes and ABR latencies were also positive even though it was statistically non-significant. This study was not supported the abnormal auditory nerve transmission time as the latencies of wave I and II were not affected significantly.

Mahalik et al. (2015) investigated the Auditory Brainstem Response (ABR) in middle aged individuals with diabetes mellitus. The study done on 25 individuals diagnosed with diabetes mellitus type 2. In participants with diabetes mellitus, ABR responses for left ear was affected in terms of delayed latencies of wave I and III where as in right ear, delayed latencies were found for wave I and V. Prolonged interpeak latency III-V was also found in diabetic group bilaterally. This was one among the study which supported the abnormal transmission time at the peripheral level as the wave I was affected significantly.

2.2.1. Speech evoked ABR in diabetics

Though utility of speech evoked ABR is still under research, many authors have tried to find its application in various clinical population. Majority of the studies of speech evoked ABR are done in language learning disabilities, auditory processing disorders, epilepsy and stuttering (Elkabariti, Khalil, Hussein & Talaat, 2014; Hornickel & Kraus, 2011; Kumar & Singh, 2015; Tahei, Ashayeri, Pourbakht & Kamali, 2014). Effect of age on speech evoked ABR has also been investigated (Vander Werff & Burns, 2011).

A recent study in Indian context by Gupta et al. (2015) investigated the speech evoked ABR responses in individuals with diabetes mellitus type 2. The study included 25 middle aged individuals with diabetes mellitus type 2 and same number of age matched controls. All the participants in the diabetic group were having the disorder from at least 5 years and they were having normal hearing sensitivity established by pure-tone thresholds. Results of this study showed that diabetic group had prolonged onset response

latencies (wave V & A) as well as sustained responses (wave D, E & F). Along with the latency measures, Amplitude of the fundamental frequency (F_0) and its harmonics (F_1 & F_2) have also shown significant reductions in diabetic groups. Though the study had attributed these findings to delay in the neuronal conduction time and brainstem dysfunctions that may affect encoding of speech processing, the authors also give a possible research direction to correlate these findings to behavioural speech perception tests as well as temporal measures.

So, across the various findings it is evident that diabetes has adverse effect on higher auditory structures and it can be tapped through click evoked ABR. The involvement of brainstem to midbrain structures are more evident than involvement of 8th nerve as most of the studies suggest that earlier peaks found to be within normal latencies inspite of prolonged latencies of later peaks (Baweja et al., 2013; Donald et al., 1981; Gupta et al., 2013; Talebi et al., 2008). The recent research attempt on using speech evoked ABR to tap the subcortical encoding of speech stimuli also found significant results (Gupta et al., 2015). However more research should be done to reach a valid finding on the utility of speech evoked ABR.

2.3. Auditory temporal processing tests

The minimal time required to segregate or resolve acoustic events in the auditory system is termed as temporal resolution (Shin & Musiek, 2003). Many psychoacoustic experimenters have quoted that poor speech perception is often contributed by reduced temporal resolution in the auditory system (Snell & Frisina, 2000; Strouse et al., 1998; Walton, 2010). Temporal resolution occurs both binaurally and monaurally. Monaural

temporal processing is more means of following a speech signal whereas binaural temporal processing gives information about separating a signal form its competing sounds (Strouse et al., 1998). Gap detection threshold (GDT) and Temporal Modulation Transfer Function (TMTF) are the common measure to assess temporal resolution (Kumar, Sangamanatha & Vikas, 2013; Miller, 2010; Narne, 2013; Strouse et al., 1998).

2.3.1. Gap detection threshold (GDT)

GDT has been considered as the simplest way of assessing temporal resolution (Samelli & Schochat, 2008). The gap detection threshold is the smallest detectable temporal gap separating the two signals. It is generally measured in terms of milliseconds. Though there is variability across studies, GDT in normal young adults have been found to be around 2 to 3 msec (He, Horwitz, Dubno & Mills, 1999; Moore, 1996). Among the various methods available, the 'Maximum Likelihood Procedure' tool box (Grassi & Soranzo, 2009) available in the MATLAB has been recently used to measure gap detection threshold reliably (Kumar et al., 2013; Kumar & Sangamanatha, 2011).

Though there is a dearth of literature regarding the gap detection thresholds in the clinical population of diabetes, there is evidence on the effect of aging on temporal resolution through gap detection thresholds (Fakruddin & Rajalakshmi, 2006; Kumar & Sangamanatha, 2011; Snell, 1997; Strouse et al., 1998). As aging is associated with neuronal degeneration at the higher auditory system abnormal gap detection threshold has been found across studies (Snell, 1997; Strouse et al., 1998). In individuals with hearing

impairment also, gap detection threshold found to be higher (Fakruddin& Rajalakshmi, 2006; Fitzgibbons & Wightman, 1982; Florentine & Buus, 1984).

2.3.2. Temporal Modulation Transfer Function (TMTF)

Modulation detection refers to the subjects' ability to find small overall changes in the amplitude of a sound (Gelfand, 2007). To assess TMTF, the modulation depth necessary to identify the change in a sinusoidally amplitude modulated noise is measured for various modulation frequencies. The modulation detection threshold is plotted as a function of modulation frequency and the resultant graph is termed as TMTF (Viemeister, 1979). Though gap detection and TMTF are quantitative measure of temporal resolution, TMTF can give information about both intensity resolution as well as temporal resolution separately (Strickland & Viemeister, 1997).

There is no literature evidence of TMTF in diabetic individuals. However few authors have tried to find the aging effect on Modulation detection (Kumar & Sangamanatha, 2011; Shen, 2014; Takahashi & Bacon, 1992). Majority of the researchers suggest that modulation detection thresholds tend to be poor as aging advances. This is more evident at higher modulation frequencies (Shen, 2014). TMTF in individuals with hearing impairment is also explored by some researchers (Bacon & Gleitman, 1992; Bacon & Viemeister, 1985; Moore, Shailer & Schooneveldt, 1992). As diabetes mellitus may lead to subclinical central neuropathy and its effect on precipitating hearing loss is also evident, it would be interesting to see how diabetes affects the modulation detection thresholds as a function of modulation frequencies.

Hence, behavioural tools are reliable measures to assess temporal processing abilities. Correlating these findings with electrophysiological measures will give valid evidence on the auditory temporal processing aspects in individuals with diabetes mellitus. The current study measures speech encoding and temporal resolution as reduced temporal resolution can often reflect in poor speech perception. A correlation between these two measures will give some valid findings in the higher auditory processing in individuals with diabetes mellitus type 2.

2.4. Histopathological changes in auditory system in diabetes mellitus

Though the association of hearing impairment and diabetes has been quite established through clinical findings of various tests, the Histopathological changes associated with the subclinical hearing loss remains unclear. Quite a few studies have tried to explore these changes through investigations in animal and human models (Costa, 1967; Fukushima et al., 2006; Ishikawa, Naito & Taniguichi, 1995; Jorgenson, 1961; Kovar, 1973; Lee, Kim, Chung, Cho & Hong, 2008; Makishima & Tanaka, 1971; Tachibana & Nakae, 1986)

2.4.1. Histopathological changes at the peripheral level

In a meta-analysis of histopathological changes in cochlea secondary to diabetes mellitus, Akinpelu, Ibrahim, Waissbluth, and Daniel (2014) reviewed 21 articles studied on histopathological changes in the diabetic auditory system. Among this 14 studies were on animal models whereas 7 studies were done on human temporal bone as well. Majority of the studies found changes at various levels of cochlea including organ of corti, Stria vascularis, Spiral ligament, and spiral ganglion neurons (Costa, 1967;

Fukushima et al., 2006; Ishikawa et al., 1995; Jorgenson, 1961; Kovar, 1973; Lee et al., 2008; Makishima & Tanaka, 1971; Tachibana & Nakae, 1986)

Organ of Corti: Studies in animal model showed loss or degeneration of outer hair cells (OHCs) and/or inner hair cells (IHCs) (Lee et al. 2008; Tachibana & Nakae, 1986) Human model study done by Fukushima et al. (2006) revealed loss of OHC in the in the presence of normal IHCs. Loss of OHC are found to be more in the in the basal turn of cochlea. These authors also revealed degeneration of OHCS as the thickening of the basilar membrane (BM) increases in long term diabetic individuals.

Stria Vascularis: Studies in mice showed widened intercellular spaces, protrusion of the marginal cells, swelling of the inter mediate cells, and degenerative changes in the marginal cells of the stria vascularis (Lee et al., 2008; Tachibana & Nakae, 1986). Human studies have also shown significant pathophysiological changes like reduction in the stria vascularis area in all cochlear turns in individuals with diabetes mellitus for a longer duration. The rate of atrophy of Stria vascularis with aging also found to be increased in diabetic individuals as compared to controls (Fukushima et al., 2006).

Spiral ligament: Study by Fukushima et al. (2005) on type 1 diabetic individuals found significant pathophysiological changes in the spiral ligament. The changes observed were include loss of fibrocytes in the cochlear, predominantly at apical and medial turns. Rate of degeneration of spiral ligament cells were also found to be more in diabetic individuals with advancing age than healthy controls.

Spiral ganglion neurons: Studies in mice as well as human models shown significant changes at the level of spiral ganglion neurons (Kovar, 1973). Animal model

studies found loss of spiral ganglion neurons along with reduction in area of the cells at the spiral ganglion majorly at the basal turn of cochlea. Kovar (1973) found similar findings in human temporal bone studies as well.

2.4.2. Histopathological changes at the central level

Although the pathophysiological changes at cochlear level is quite known, the central pathological lesion is relatively unknown. The clinical correlates of delayed responses at the brainstem level through ABR responses and nerve conduction studies are yet to be unknown. Makishima & Tanaka (1971) reported degenerative changes at the central auditory pathway as the major pathophysiological findings. The exact mechanism behind these neuronal degeneration in diabetes mellitus remains unknown. However, a recent study report that insulin resistance in diabetics leads to compromise in cell survival, metabolism and neuronal plasticity, increased oxidative stress and apoptosis of neurons etc. (de la Monte, Longato, Tong & Wands, 2009). A dual pathological mechanism including silent infarct and metabolic disturbances as the explanations of these findings were also proposed. (Huang et al., 2010; Kurita, Mochio & Isogai, 1995).

Though, exact underlying pathophysiological mechanism of central neuropathy in diabetes mellitus is relatively unknown, at the peripheral level it is relatively known. The current study does not aim on finding the pathophysiological mechanism in the auditory system. But it is important to attribute the result findings to the underlying pathologies.

Chapter 3

Method

3.1. Participants

The current investigation comprised of 35 participants divided into four groups.

Group I: 10 adults (20 ears) in the age range of 40 to 60 years (Mean age - 50.1 years) with no history of diabetes mellitus type 2 and hearing sensitivity within normal limits.

Group II: 10 adults (20 ears) in the age range of 40 to 60 years (Mean age - 49.9 years) with diabetes mellitus type 2 and hearing sensitivity within normal limits.

Group III: 10 adults (20 ears) with mild-to-moderate sensorineural hearing loss and no history of diabetes mellitus type 2 in the age range of 40 to 60 years (Mean age – 50.8 years).

Group IV: 5 adults (10 ears) with mild-to-moderate sensorineural hearing loss and diabetes mellitus type 2 in the age range of 40 to 60 (Mean age - 52.8 years) were participated in the study.

3.1.1. Participant selection Criteria

Among the four groups studied, group I and II were having individuals with normal hearing sensitivity whereas group III and IV were comprised of individuals with mild-to-moderate sensorineural hearing impairment (See figure 2.1). Group II and IV were considered as experimental group as they had diabetes mellitus at least from last 5 years. Among this, group II had individuals with normal hearing sensitivity as well as diabetes mellitus type 2. Group IV had individuals with mild-to-moderate sensorineural

hearing impairment and history of diabetes mellitus type 2 since last 5 years. Further, age matched participants without history of diabetes mellitus were served as the control group. The control group subjects were also divided into two groups. Group I had only individuals with hearing sensitivity within normal limits and no history of diabetes and were served as the control group. Similarly, group III had individuals with mild-to-moderate hearing impairment and no history of diabetes and served as another control group. All the groups' participants had normal middle ear functions as per immittance audiometry. The diagnosis of diabetes mellitus was confirmed by a physician based on the blood glucose measurements including average blood sugar level over the previous three months (HbA1C), along with random and fasting blood sugar level of the individual. Those participants who had any history of neurological problems were excluded from the study. All the participants were signed with an informed consent to participate in the study and they were enrolled in a non-payment basis.

3.2.Testing environment

All the basic audiologic, psychoacoustic as well as electrophysiological tests were carried out in a sound treated room where the noise levels were as per the guidelines in ANSI S3.1 (1999). Pure-tone audiometry were carried out in a two room set up whereas psychoacoustic measures and electrophysiological testing were done in a single room suite. The testing rooms were well illuminated.

3.3.Instrumentation

A calibrated two channel clinical audiometer (GSI Audiostar Pro) with TDH-39 headphones housed in MX-41/AR ear cushions were used for pure tone audiometry.

Radioear B-71 bone vibrator was used for measuring bone conduction threshold. A calibrated middle ear analyzer (GSI Tympstar) using 226 Hz probe tone was used for tympanometry and reflexometry. For recording click and speech evoked ABR, Biologic Navigator Pro (version 7.0) with ER-3A insert receiver was used. Behavioural temporal processing tests were administrated using a personal computer installed with MATLAB software (Version 2010a). This laptop was coupled with a calibrated Sennheiser HDA 200 circumaural headphone for stimulus presentation.

3.4. Procedure

The present study involved two stages. Stage 1 involved basic audiological tests meant for the participant selection criteria. Experimental tools were administered in Stage 2 which involved electrophysiological tests and behavioural temporal measures. All testing were carried out in a single session. However, participants were given time break in between the tests depending on their requirements.

3.4.1. Stage 1

The preliminary stage of the study included basic audiological evaluation. Pure tone thresholds were obtained using modified version of Hughson and Westlake procedure (Carhart & Jerger, 1959) across octave frequencies from 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz and 8000 Hz for air conduction and frequencies from 250 Hz to 4000 Hz for bone conduction. Along with pure-tone audiometry, speech recognition threshold (SRT), word recognition score (WRS) were obtained using live monitored speech. Speech audiometry was done in subject's native language and spondee words were used for SRT whereas phonetically balanced words were used for WRS.

Immittance audiometry were carried out with a probe tone frequency of 226 Hz. Acoustic reflexes thresholds for both ipsilateral and contralateral measures were obtained at 500 Hz, 1000 Hz, 2000Hz, and 4000 Hz. Only participants with 'A' type tympanogram and presence of acoustic thresholds were considered for the study.

Based on the audiological outcomes subjects were assigned to respective groups. Subjects with normal hearing sensitivity were assigned into group I and group II respectively. Subjects with Mild-to-moderate sensorineural hearing loss were assigned into group III and group IV.

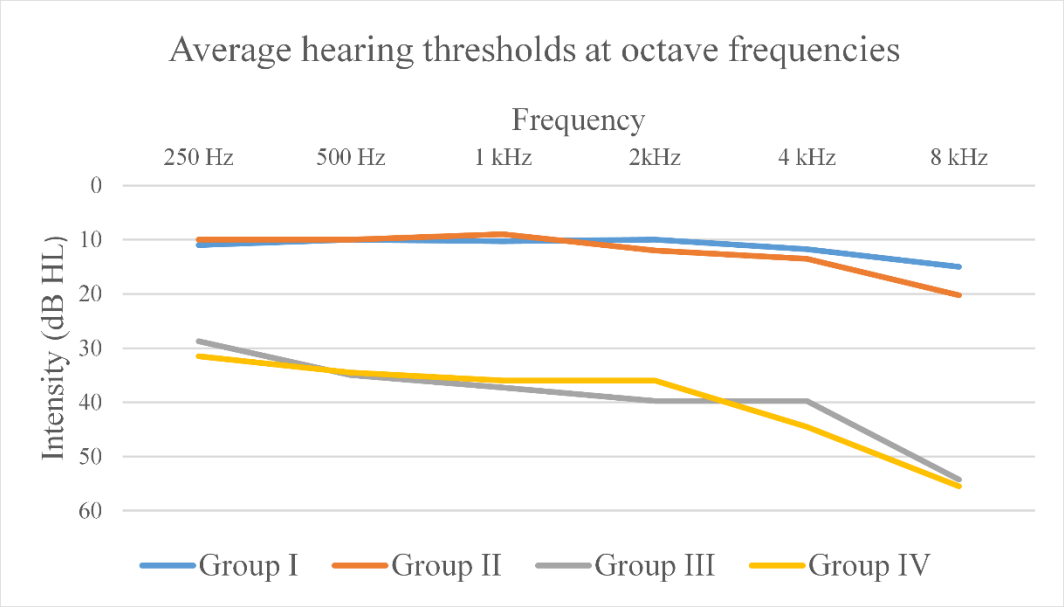

Figure 3:1: Average audiometric thresholds of all groups at octave frequencies for all groups (Group I; Group II; Group III; Group IV)

3.4.2. Stage 2

Stage 2 of the data collection involved administration of major experimental tools. The present study used electrophysiological as well as behavioural temporal measures.

The main electrophysiological measure of the study was speech evoked ABR. Prior to speech evoked ABR, click evoked ABR were also done to validate the integrity of auditory system and to rule out the retro-cochlear pathology. Psychoacoustic tools were used to investigate the temporal processing abilities of the participants. Gap Detection Threshold (GDT) and Temporal Modulation Transfer Function (TMTF) were the temporal measures used in the current study. Procedure of the various tests used in the study are explained below.

3.4.2.1. *Electrophysiological tests*

The electrophysiological tests were done by making the participants sitting in a reclining chair. Subjects were advised to avoid any extraneous movements of the body parts during the tests in order to prevent muscular artefacts. The absolute electrode impedance and inter-electrode impedance were maintained below 5 kΩ and 2 kΩ respectively. Silver chloride electrodes were used to record the responses. Recording was done monaurally and ipsilaterally with electrodes at vertex (non-inverting), ipsilateral mastoid (Inverting) and contralateral mastoid (Ground). The electrode placement were same for click evoked ABR and speech evoked ABR. Both tests were carried out at 50 dBSL with reference to pure tone average (PTA).

Click evoked ABR: Click evoked ABR was evaluated to check the integrity of neural pathway at the levels of brainstem prior to measure the speech evoked ABR. The click evoked ABR elicited using a 100 μsec presented ipsilaterally through Etymotic ER-3A insert earphones. The artefact rejection value was kept at 35μv. The responses were band pass filtered between 100 Hz to 3000 Hz and amplified by 100000 times. The

analysis window of the responses were kept as 10 msec along with 2 msec pre-stimulus time. Total number of averages were 1500.

Speech evoked ABR: The speech evoked ABR was recorded for all the participants with speech stimuli /da/ of 40 ms duration produced using KLATT synthesizer (Klatt, 1980). At least two recordings of 3000 sweeps to alternating polarity at a rate of 10.9/s were collected. The responses were amplified 100000 times and weighted addition of the two recordings were taken for analysis. Time window of 64 ms including 10 ms pre-stimulus time was used. The responses were band pass filtered online between 100 to 2000 Hz.

3.4.2.2. *Behavioural Temporal tests*

Temporal processing tests administrated in the current study are GDT and TMTF. Both the tests were done using the psychoacoustic tool box in MATLAB which implements the 'Maximum Likelihood Procedure' (MLP) originally given by Green (1990, 1993). The maximum likelihood procedure is an adaptive procedure for threshold estimation. Based on various subject psychometric functions it calculates the probability of obtaining the listener's response to all of the stimuli that have been presented given each psychometric function. The psychometric function yielding the highest probability determines the stimulus to be presented on the next trial. A three interval alternate forced choice (3AFC) method using MLP were adopted to find the correct response criterion of 80%. In a 3AFC paradigm, at each trial there were three stimuli and among these, two intervals were contained a reference stimuli, and the other interval contained the variable stimulus. After each trial, the individual had to say which interval had the variable

stimulus. The mode of response was verbal or non-verbal depending on the subject' preference. The testing administrated in one block which included 30 trials. The above mentioned procedures are common for both GDT and TMTF.

Gap Detection Test (GDT): GDT was used as one of the test to assess the temporal resolution of the individuals. The subjects had to identify a temporal gap in a white noise which is of 750 ms duration (Standard stimulus). The noise was band pass filtered between 400–1600 Hz. This white noise was ramped (0.5 msec) at the beginning and end of the gap. A 3AFC method was used, where duration of temporal gap was varied (variable stimulus) based on the subject response.

Temporal Modulation Transfer Function (TMTF): TMTF was used to find the modulation detection threshold in an amplitude modulated white noise. The subjects' task was to identify the interval containing the amplitude modulation in a 3AFC paradigm using MLP procedure. The stimuli used in the current study was a 500 msec Gaussian noise of 500 msec duration (Standard stimuli) with cosine ramp of 10 msec. This signal was sinusoidally amplitude modulated at four modulation frequencies (8 Hz, 20 Hz, 60 Hz & 200 Hz). Modulation detection threshold at each modulation frequency were determined. The depth of the modulation was varied on the variable stimuli depending on the subjects' response at each trial to achieve the 80% correct response criterion. The modulation detection thresholds were based on the modulation depth in decibels (20xlog10 (m)).

3.5. Statistical Analysis

Statistical analysis were done using Statistical Package for the Social Sciences (SPSS - version 20.0). Mean and standard deviation were obtained through descriptive statistical analysis. Multivariate analysis of variance (MANOVA) were used for within and between group comparisons of the latency of click ABR, Speech ABR and TMTF. Fast Fourier Transform (FFT) measures of speech evoked ABR were analysed using Kruskal - Wallis test for comparison between group I and II as well as group III and IV. Independent‘t’ test were done for comparison of group I and II as well as group III and IV for gap detection threshold.

Chapter 4

Results

The current study included four groups of participants. Group I and II comprised of normal hearing individuals without and with diabetes mellitus type 2 whereas group III and IV included individuals with hearing impairment without diabetes and with diabetes respectively. Across group comparison were done between group I and II as well as group III and IV. All the subjects were assessed with electrophysiological (Click ABR & Speech evoked ABR) and behavioural tools (gap detection threshold and temporal modulation transfer function).

4.1. Electrophysiological Measures

Electrophysiological measures included click evoked ABR and speech evoked ABR, which were analysed in terms of latency and amplitude parameters of different components of both the tests.

4.1.1. Latency measures of Click evoked ABR

For the click ABR, absolute latency of wave I, wave III, and wave V along with inter-peak latencies of I-III, III-V and I-V were calculated (Table 4.1). When comparison between group I and II were done using MANOVA, there was significant difference in the absolute latencies of wave I [F (1, 38) = 7.57; p = 0.01; partial eta squared = 0.16] and V [F (1, 38) = 8.62; p = 0.01; partial eta squared = 0.18] and difference for wave III was marginal [F (1, 38) = 3.85; p = 0.05; partial eta squared = 0.09] between the groups. However, Inter-peak latencies I-III [F (1,38) = 0.62; p = 0.43; partial eta squared = 0.01], III-V [F(1,38) = 3.04; p = 0.08; partial eta squared = 0.07], and I-V [F(1,38) = 0.27; p =

0.60; partial eta squared = 0.01] did not shown any significant differences between group I and II.

Similarly, when comparison were made between group III and IV, MANOVA outcomes showed no significant difference between any of the absolute and inter-peak latencies of click evoked ABR. Wave I [F (1,28) = 1.90; p = 0.17; partial eta squared = 0.06], Wave III [F (1,28) = 1.87; p = 0.18; partial eta squared=0.06] and Wave V [F (1,28) = 1.09; p = 0.30; partial eta squared= 0.03] had no significant difference between both the groups. Simillar trend was observed for interpeak latencies I-III [F (1, 28) = 0.36; p= 0.55; partial eta squared = 0.01], III-V (F (1, 28) = 0.22; p = 0.55; partial eta squared = 0.01] and I-V [F (1, 28) = 0.11; p = 0.74; partial eta squared = 0.00] as there no significant differences between group III and IV.

Table 4.1: Mean and standard deviation of latency measures of click evoked ABR

Peak	Group 1 n=20		Group 2 n=20		Group 3 n=20		Group 4 n=10	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I	1.76	0.15	1.97	0.29	1.97	0.23	1.93	0.16
III	3.74	0.18	3.86	0.20	3.85	0.27	3.97	0.08
V	5.68	0.19	5.90	0.26	5.64	0.47	5.81	0.28
I-III	1.97	0.21	1.91	0.25	2.22	0.93	2.04	0.21
III-V	1.94	0.18	2.04	0.18	1.89	0.15	1.85	0.27
I-V	3.91	0.26	3.95	0.25	3.88	0.25	3.92	0.34

n,,number of ears; SD- standard deviation

4.1.2. Latency and Amplitude measures Speech evoked ABR

Speech evoked ABR responses were measured for all the four group of subjects using the conventionally used /da/ stimulus. The responses analysed include latency of V, A, D, E, F and O along with amplitude of the fundamental frequency (F_0), first formant

(F_1) and second formant (F_2). Latency measures were done by visual analysis whereas amplitude of the fundamental frequency and higher formants were analysed using the MATLAB based brainstem toolbox. Responses rate for wave V, A, D, E, F were 100 % for all the groups.

Descriptive statistics used to obtain the mean and standard deviation (SD) of latency measures as well as amplitude of the steady state portion of the response. From Table 4.2, it is noticed that, latency of group II is higher (prolonged) than group I. Similarly group IV shows prolonged latency compared to group III. The amplitude of F0, F1, and F2 are lesser for group II and group IV in comparison to group I and III respectively (Table 4.3).

Table 4.2: Mean and standard deviation of latency measures of speech evoked ABR

	Group 1 n=20		Group 2 n=20		Group 3 n=20		Group 4 n=10	
Peak	Mean	SD	Mean	SD	Mean	SD	Mean	SD
V	6.53	0.61	6.82	0.60	6.43	0.42	6.18	0.31
A	7.56	0.68	7.88	0.67	7.59	0.65	7.86	0.60
D	22.82	1.70	24.10	1.39	23.11	1.38	24.10	1.74
E	31.58	1.29	32.99	2.30	31.20	1.55	31.83	1.57
F	40.37	1.62	41.25	2.36	40.20	1.82	40.06	1.48
O	47.67	1.55	49.42	2.22	49.02	2.67	50.44	1.49

n, number of ears; SD – standard deviation

Table 4.3: Fast fourier transform (FFT) analysis of speech evoked ABR

Amplitude	Group 1 n=20		Group 2 n=20		Group 3 n=20		Group 4 n=10	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
F0	5.34	1.79	3.71	2.53	10.03	7.36	5.85	2.41
F1	0.66	0.37	0.55	0.17	1.19	0.51	0.96	0.66
F2	0.275	0.27	0.29	0.29	0.32	0.32	0.29	0.09

n,,number of ears; SD- standard deviation

4.1.1.1. *Comparison of Speech evoked ABR between group I and II*

Group I and II were comprised of non-diabetic normal hearing individuals and diabetic normal hearing individuals respectively. Individual waveforms (A) and Grand average of the waveforms (B) of groups I and II is shown in figure 4:1 and 4:2 respectively.

The transient portion of speech evoked ABR i.e. wave V and A were measured in terms of its latency. MANOVA outcomes of the comparison between two groups suggestive of no significant differences among the latencies of wave V [F (1, 38) = 2.23; p = 0.14; partial eta squared = 0.05] and A [F (1, 38) = 2.22; p = 0.14; partial eta squared= 0.05]. However, responses to the steady state portion of the stimuli has shown significant differences for latencies of wave D [F (1, 38) = 6.71; p = 0.01; partial eta squared=0.15] and E [F (1, 38) = 5.61; p = 0.02; partial eta squared = 0.12] but this trend did not followed for later peak F [F (1, 38) = 1.85; p = 0.18; partial eta squared = 0.04]. The offset component O [F (1, 38) = 8.49; p = 0.00; partial eta squared = 0.18] has also shown significant difference between the two groups.

Amplitude of the sustained responses such as F_0, F_1, and F_2 were analysed using Kruskal-Wallis test. There was a significant difference between amplitude of the F_0 [χ^2 (1) = 4.56; p = 0.00]. However, higher formant frequencies i.e. F_1 [χ2 (1) = 0.21; p = 0.64] and F_2 [χ2 (1) = 0.37; p = 0.54] did not show any significant differences between the two groups.

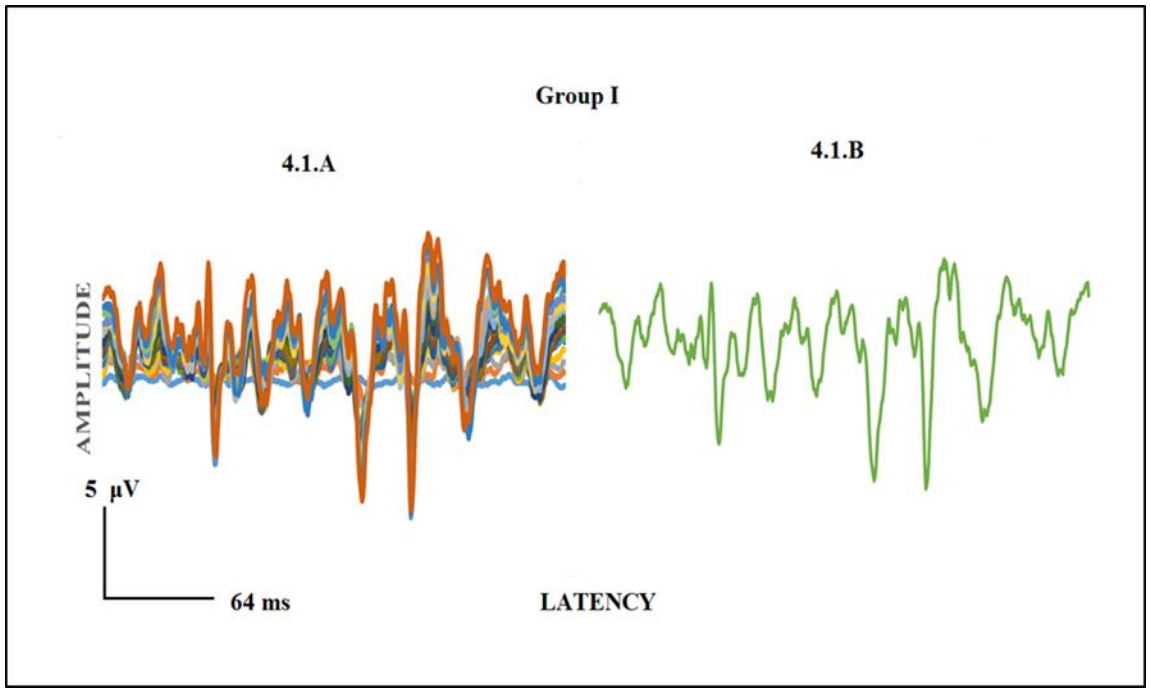

Figure 4:1: Individual waveforms (4.1.A) and grand mean average waveform of the speech evoked ABR of group I

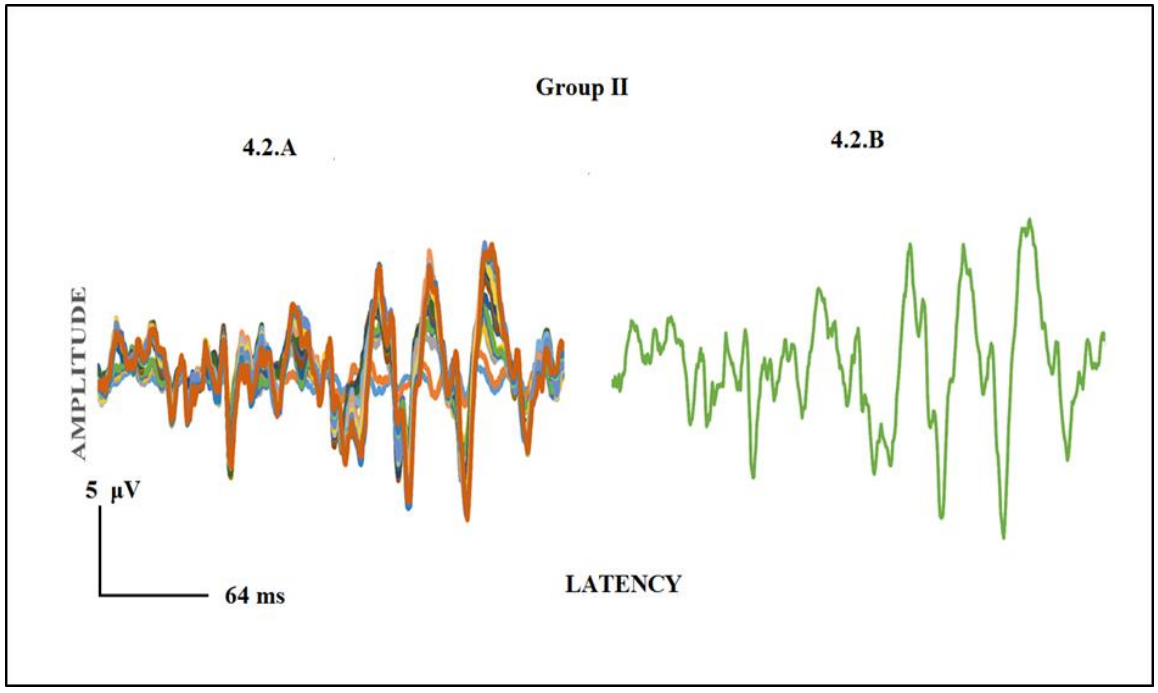

Figure 4:2: Individual waveforms (4.2.A) and grand mean average waveform (4.2.B) of the speech evoked ABR of Group II

4.1.1.2. *Comparison of speech evoked ABR between group III and IV*

Group III and IV comprised of non-diabetic hearing impaired individuals and diabetic hearing impaired individuals respectively. Individual waveforms (A) and Grand mean average waveforms (B) of the speech evoked ABR are shown in Figure 4:3 and 4:4 respectively. MANOVA was used to check the comparison between group III and IV. Results of latency measures of wave V [F (1, 28) = 2.67; p = 0.11; partial eta squared = 0.087] and A [F (1, 28) = 1.22; p = 0.27; partial eta squared = 0.04] had no significant difference between the groups. The sustained portion of the response has also shown no significant differences across both the groups; wave D [F (1, 28) = 0.92; p = 0.34; partial eta squared = 0.03]; wave E [F (1, 28) = 1.07; p = 0.30; partial eta squared=0.03] and wave F [F (1, 28) = 0.04; p = 0.83; partial eta squared = 0.00]. The offset response i.e. wave O [F (1, 28) = 2.41; p = 0.13; partial eta squared = 0.07] also did not show any significant differences between group III and IV. FFT analysis of amplitude of F_0 [$\chi 2$ (1) = 1.51; p = 0.21], F_1 [$\chi 2$ (1) = 1.21; p = 0.27] and F_2 [$\chi 2$ (1) = 0.93; p = 0.33] were also not shown significant difference between the two groups, comprising of hearing impaired individuals with and without diabetes mellitus type 2.

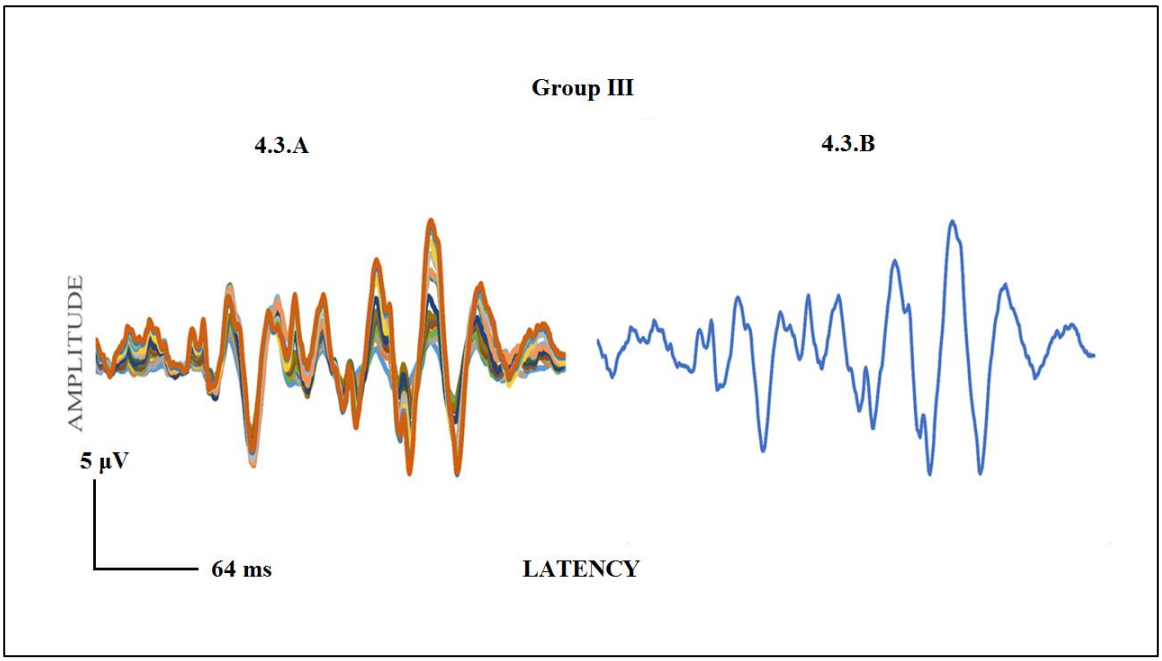

Figure 4:3: Individual waveforms (4.3.A) and grand mean average waveform (4.3.B) of the speech evoked ABR of Group III

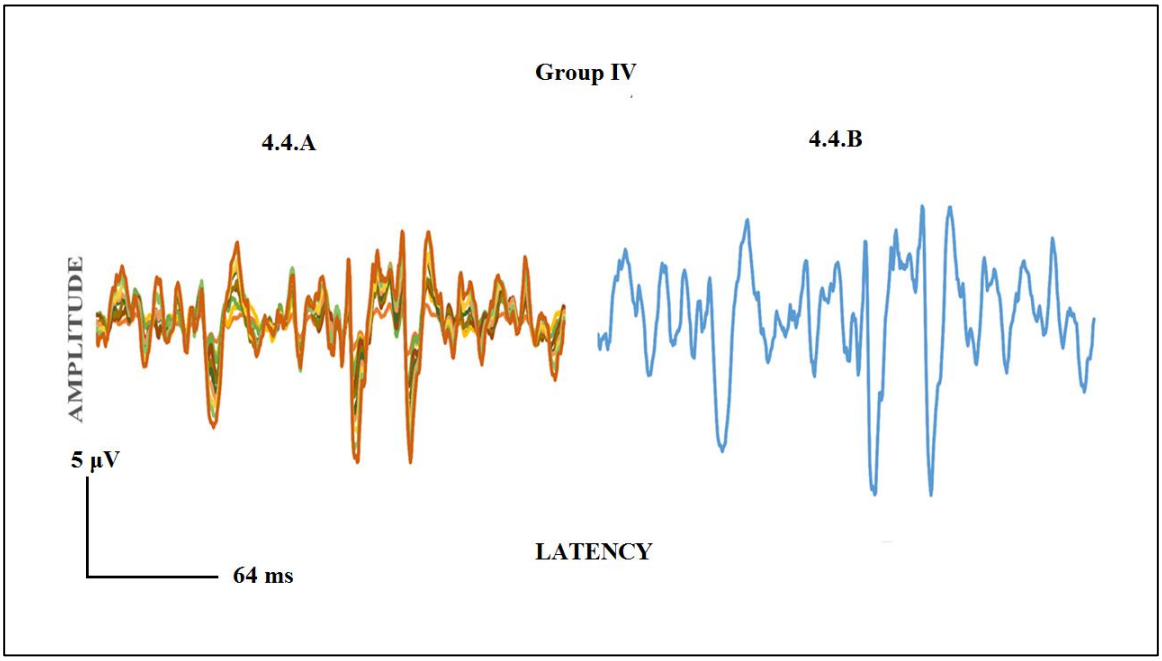

Figure 4:4: Individual waveforms (4.4.A) and grand mean average waveform (4.4.B) of the speech evoked ABR of Group IV

4.2. Behavioural Temporal Measures

Along with the electrophysiological measures, behavioural tests to assess auditory temporal processing were also administrated on these subjects. Gap detection threshold (GDT) and Temporal Modulation Transfer function (TMTF) were selected as the tools as these are the commonly used tests to assess temporal processing.

Mean and standard deviation of the GDT of all the groups are shown in table 4.4. Further comparison between group I and II as well as group III and IV were done. Table 4.4 shows gap detection thresholds in group II were poorer (higher) in comparison to group I. Independent 't' test outcome shows there is highly significant differences between group I and II in terms of Gap Detection threshold [t(38) = 4.88; p = 0.00]. However, Group III and IV did not show significant difference between the groups in terms of GDT [t (28) = 4.77; p = 0.63]. Though mean GDT of group IV found to be better (lesser) than group III, the SD of group IV was higher than group III, which probably indicates heterogeneity among group IV participants.

Table 4.4: Mean and standard deviation of GDT for all groups

	Group I n=20		Group II n=20		Group III n=20		Group IV n=10	
GDT	Mean	SD	Mean		Mean	SD	Mean	SD
	5.093	0.948	7.053	1.521	9.451	2.301	8.980	3.010

n,,number of ears; SD- standard deviation

TMTF were done at four modulation frequencies (8 Hz, 20 Hz, 60 Hz & 200 Hz). Mean and standard deviation of the modulation detection threshold at each modulation frequency are shown in Table 4.5. From table 4.5, it is inferred that as modulation frequencies, the temporal resolution abilities becomes poorer irrespective of the groups. At 200 Hz, the mean modulation detection threshold for all groups were poorer in comparison to other modulation frequencies.

Table 4.5: Mean and standard deviation of modulation detection threshold at different modulation frequencies (8 Hz,20 Hz, 60Hz & 200 Hz) for all groups

Modulation frequency	Group-I n=20		Group-II n=20		Group-III n=20		Group-IV n=10	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
8 Hz	-28.61	4.14	-30.22	2.88	-27.14	4.56	-25.91	4.04
20 Hz	-27.83	4.20	-29.06	4.14	-24.25	6.96	-26.28	6.00
60 Hz	-17.62	6.34	-18.47	3.26	-12.88	6.96	-14.39	7.31
200 Hz	-11.95	4.84	-8.41	5.21	-7.46	2.79	-3.05	5.43

n,,number of ears; SD- standard deviation

Comparison between group I and II using MANOVA suggestive of no significant differences at lower modulation frequencies such as 8 Hz [F (1, 38) = 2.05; p = 0.16; partial eta squared = 0.05], 20 Hz [F (1, 38) = 0.86; p = 0.35; partial eta squared = 0.02] and 60 Hz [F (1, 38) = 0.28; p = 0.35; partial eta squared = 0.00]. However, there was a significant difference at a relatively higher modulation frequency 200 Hz [F (1,38) = 4.97; p = 0.03; partial eta squared = 0.11] between group I and II.

Modulation detection threshold were also compared between group III and IV individuals. As like the normal hearing individuals, there was no significant differences at lower modulation frequencies such as 8 Hz [F (1, 28) = 0.51; p = 0.47; partial eta

squared=0.01], 20 Hz [F (1, 28) = 0.61; p = 0.440; partial eta squared = 0.02] and 60 Hz [F (1, 28) = 0.30; p = 0.58; partial eta squared = 0.01]. But significant difference were obtained at 200 Hz [F (1, 28) = 8.75; p = 0.01; partial eta squared = 0.23] between group III and IV.

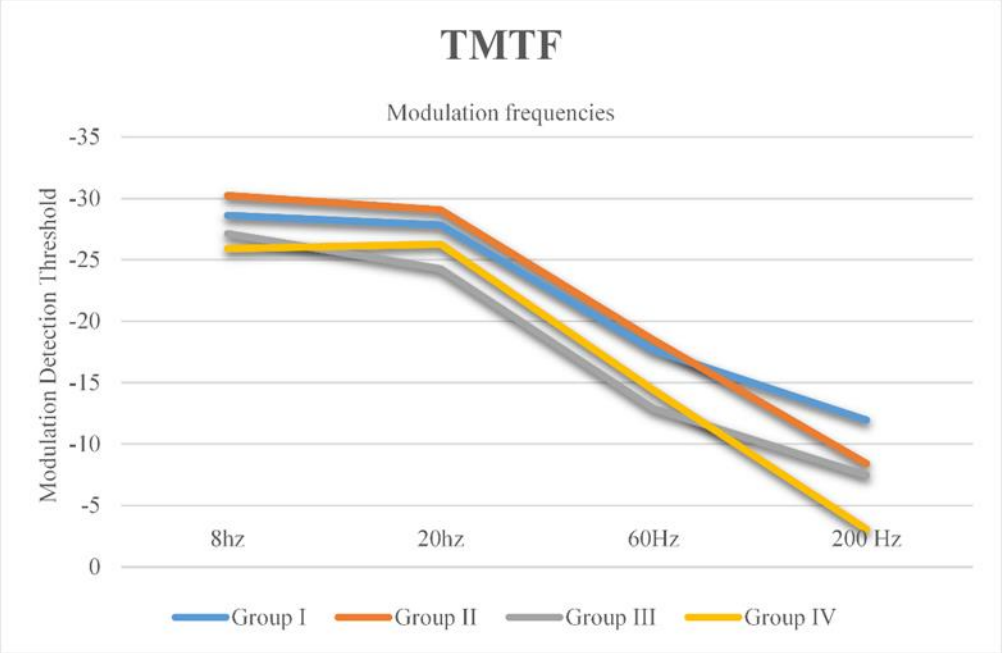

Figure 4:5: Modulation detection threshold at different modulation frequencies (8Hz, 20 Hz, 60 Hz & 200Hz) for all groups

Chapter 5

Discussion

The purpose of the current study was to see the speech processing at the brainstem level as well as the auditory temporal processing in individuals with diabetes mellitus type 2. The current study compared the electrophysiological measures (Click ABR & Speech ABR) and behavioural temporal measures (GDT & TMTF) in individuals with diabetes mellitus type 2 and age matched individuals with no history of diabetes mellitus. Various measures of electrophysiological and behavioural measures were compared between the groups using suitable statistical tests.

5.1. Latency measures of click evoked ABR

Latency measures of click ABR analysed in the current study are absolute latencies of wave I, wave III, and wave V along with interpeak latencies wave I-III, III-V, and I-V. The response rate of all the peaks were 100% in all the individuals.

5.1.1. Comparison between group I and II

Group I and II were comprised of normal hearing individuals without diabetes mellitus and with diabetes mellitus. Several studies compared click ABR in individuals with diabetes mellitus and non-diabetic individuals (Baweja et al., 2013; Donald et al., 1981; Gupta et al., 2013; Konrad-Martin et al., 2010; Mahallik et al., 2014). The findings of present study suggests that latency of wave I and V were significantly prolonged in individuals with diabetes mellitus and the difference in the latency of wave III was marginal. Prolongation of wave III and V in individuals with diabetes mellitus were reported in many of the previous literatures (Baweja et al., 2013; Donald et al., 1981;

Gupta et al., 2013; Vaughan, James, McDermott, Griest, & Fausti, 2007). However, prolongation of wave I in diabetic individuals is not evident in majority of the existing literature (Baweja et al., 2013; Donald et al., 1981; Gupta et al., 2013; Vaughan et al., 2007). Donald et al. (1981) suggested the involvement of a central lesion in the presence of normally functioning auditory nerve. The pathological lesion may specifically correlates to the transmission delay at the collicular level, probably from brainstem- to-midbrain. Histopathological findings of the higher order structures in long term diabetic individuals shows diffuse degeneration of ganglion cells and nerve fibers at the brainstem and cortical levels (Reske-Nielson & Lundbaek, 1975).

However, study by Mahalik et al. (2015) found delay in wave I along with the later peaks. Findings of the current study were also supported by Bayazit, Yilmaz, Kepekci, Mumbuc & Kanlikama (2000), where they found significant prolongation in the absolute latencies of wave I and wave V. Delay in absolute latency of wave I can be attributed to prolonged transmission at the level of auditory nerve. This could be due to the neural pathology associated with diabetes mellitus.

5.1.2. Comparison between group III and IV

Majority of Studies investigated the click evoked ABR in diabetic individuals were excluded the participants with hearing impairment (Baweja et al., 2013; Donald et al., 1981; Gupta et al., 2013; Vaughan et al., 2007). Since it is quite evident that hearing impairment can be one among the subclinical complication of diabetes (Cullen & Cinnamond, 1993; Kakarlapudi et al.,2003; Panchu, 2008; Rajendran et al., 2011), so the current study also investigated click evoked ABR in diabetic individuals with hearing

impairment. Group III consisted of individuals with hearing impairment without diabetes mellitus whereas group IV included diabetic individuals with hearing impairment. The average pure tone average (PTA) of group III was 37. 93 dBHL and group IV was 37.75 dBHL. All the individuals had either mild or moderate sensorineural hearing loss in both ears.

The findings of the current study shows no significant difference between any of the latency measures of both the groups. This finding is in contrast with Konrad- martin et al. (2010) where they reported click ABR abnormalities reflected by prolonged latencies in wave III and wave V in diabetic individuals compared to non-diabetic individuals irrespective of hearing impairment. Considering the restricted evidence from literature, the effect of hearing loss in the click ABR latencies in individuals with diabetes mellitus is yet to be explored. The reason behind comparable latencies between the two groups of the current study is unable to explain by the authors. The authors of the present study believe that more research should be done on this aspect to explore the effect of peripheral hearing loss on click ABR in individuals with diabetes mellitus.

5.2. Latency and Amplitude measures of speech evoked ABR.

The speech evoked ABR results were obtained for all the groups. Latency measures were analysed for transient and sustained measures obtained for speech ABR. However amplitude measures were only done for frequency following responses of the sustained components of the measures. Considering the large variability of the amplitude on wave V and A, and that may also dependent on the physical status of patient during testing, those are not considered for interpretation.

5.2.1. Comparison between group I and II

The present study showed comparatively prolonged latencies in group II compared to group I. However, difference between the groups were not evident in the MANOVA outcomes of transient peaks V and A. Among the sustained measures significant differences were obtained for wave D and E. Prolongation of wave F was not significant in the MANOVA outcomes. The findings of the current study is partly in support with the existing literature (Gupta, Bhat & Kumar, 2015).

Gupta et al. (2015) found significant prolongation of various components of speech evoked ABR including V, A, D, E, and F in individuals with diabetes mellitus compared to the age matched control group. Wave C and O were not analysed in the study. The difference in the prolongation of latencies were statistically significant for all the peaks. However in the current study we got statistical significance for only wave D, E and O. Though we did not obtained peak C in majority of the participants, offset component 'O' was present in all the individuals in both the groups. In spite of similarities in both the studies in terms of stimuli /da/ used, the slight difference in the findings may attributed to the difference in sample size. The present study used a relatively small sample size compared to the investigation by Gupta et al. (2015). However, it is evident that abnormalities found through click evoked ABR in individuals with diabetes mellitus is also tapped in speech evoked ABR.

Objective analysis of frequency following response showed significant reduction of F_0 in both the groups whereas amplitude of F_1 and F_2 showed no significant

differences. In Gupta et al. (2015) study, they found significant difference in reduction F_0 amplitude along with F_1 and higher formants.

5.2.2. Comparison between group III and IV

Since we have taken up an additional group of individuals with hearing impairment and diabetes, it was interesting to see whether the difference in latency and amplitude measures of speech evoked ABR also existing in these groups as well. However we had not found any significant difference between group III and IV. This finding was also same for click evoked ABR in the present study. The amplitude measures of F_0, F_1 and F_2 were highly variable in both the groups compared to individuals with normal hearing (group I & II). Administration of Kruskal-Wallis test found no significant difference between the two groups.

5.3. Auditory temporal processing measures

Behavioural measures to assess auditory temporal processing in individual with diabetes mellitus is a new research idea. As per literature, auditory temporal processing has not been investigated in diabetic individuals with behavioural measures. However, McCrimmon et al. (1997) studied the effect of hypoglycaemia in non-diabetic individuals. The study used test of basic auditory capabilities to assess temporal order judgement and simple auditory processing tasks such as pitch discrimination and loudness discrimination. Findings of the study revealed that hypoglycaemia causes significant deterioration in auditory temporal processing and loudness discrimination abilities. So it is evident that glucose dependant metabolic disorders can cause higher auditory processing disorders and it can be measured through behavioural tests. The

current study used GDT and TMTF as measures to assess temporal processing in individuals with diabetes mellitus.

5.3.1. Gap Detection Threshold (GDT)

GDT between group I and II as well as group III and IV were compared. Independent‘t’ test outcome of group I and II shows elevated (poorer) GDT in group II and it was statistically significant (p = 0.00). The mean GDT of group I is in comparison with the existing literatures (Kumar & Sangamanatha, 2011; Snell, 1997). Poor GDT obtained in the group II reveals that there is underlying pathology at the subcortical level in these individuals. The auditory nerve as well as higher brainstem has significant role in encoding the gap in a stimuli (Frisina, 2001). The finding obtained in the current study is relatively new and it can be assumed that, though individuals with diabetes mellitus have normal hearing sensitivity at the peripheral level, the higher auditory structures can be more vulnerable as a subclinical complication of the disease.

However, comparison between group III and IV were not shown any significant difference. Though, the presentation of the stimuli were carried out at equal sensation level (SL), the effect of hearing loss is evident in group III and IV as their GDT value is higher when compared to group I and II. Standard deviation was also high in these groups. It is known that GDT is poorer in hearing impaired listeners compared to normal hearing individuals (Fitzgibbons & Wightman, 1982). However, it should be noted that there was no effect of diabetes on gap detection threshold in the hearing impaired population in the present study. The current study had a small sample size in group IV compared to group III and the heterogeneity in both groups were also high as reflected by

standard deviation. The authors believe this variability could be the reason to the findings obtained. Considering this is a preliminary study investigated temporal processing through behavioural measures in individuals with diabetes and hearing impairment, we believe more research should be done on a large sample size.

5.3.2. Temporal Modulation Transfer Function (TMTF)

TMTF was administrated in four modulation frequencies (8 Hz, 20Hz, 60 Hz & 200Hz). At lower modulation frequencies, there was no significant difference between group I and II as well as group III and IV. However, at 200Hz, there was a poor modulation detection threshold in diabetic individuals compared to their age matched counter parts. This findings were evident in group II as well as in group IV. As like GDT, the heterogeneity in hearing impairment group were higher in comparison to normal hearing group.

In all the group there was a trend that as the modulation frequency increases, the modulation detection thresholds became poor. This finding is in support with the existing literature (Kumar & Sangamanatha, 2011; Kumar et al., 2013; Miller, 2010). The deficit in temporal resolution in diabetic individuals were not evident at lower modulation frequencies (8 Hz, 20Hz & 60 Hz). However, at higher modulation frequency they had poor thresholds compared to non-diabetic individuals. So it may assumed that individuals with diabetes mellitus have difficulty in temporal resolution and it can be tapped through TMTF as well.

Chapter 6

Summary and Conclusion

The focus of this investigation was to see how individuals with diabetes mellitus type 2 process the speech stimuli at the brainstem level as well as to assess their temporal resolution abilities. Conventionally used research tools have been administrated to tap these abilities. To assess speech encoding, speech evoked ABR with /da/ stimuli was used whereas gap detection threshold and temporal modulation transfer function (TMTF) was used to assess temporal resolution. A total of 35 individuals (70 ears) were participated, they were divided into four different groups depending on presence or absence of diabetes and hearing impairment. Individuals with normal hearing were included in group I (non-diabetic) and II (Diabetic) whereas individuals having hearing impairment were included in group III (non-diabetic) and group IV (diabetic).

The finding of the present study suggests that speech evoked ABR can be used as a clinical non-invasive tool to tap the brainstem neuropathy and can be used as a supplemental tool to click evoked ABR. Differences in the groups were significant in terms of onset and offset responses to the stimuli, temporal and phase-locking properties of the sustained portion of the stimuli including fundamental frequency and its harmonics inspite of having normally assessed peripheral functions. An advantage of speech evoked ABR compared to click evoked ABR is that it uses a more relevant stimuli to speech perception. Though its test protocol and parameters have to be optimised to implement it as a valid tool, the findings of the preliminary research shows positive findings in the

clinical population. However caution is guaranteed to validate these findings in a large clinical population.

Along with electrophysiological measures, the present study also assessed the temporal resolution abilities through behavioural measures. Gap detection threshold in diabetic individuals were higher compared to non-diabetic individuals. This may attributed to the vulnerable cells in the higher auditory system responsible for the encoding of temporal gap in diabetic individuals. However we couldn't find a significant difference in the hearing impaired population across diabetic and non-diabetic individuals. The other tool used in the present study was TMTF. Though there was no deficit revealed at lower modulation frequencies, the findings revealed that at higher modulation frequency, diabetic individuals have poorer thresholds.

These findings suggests that middle aged individuals with long-term diabetes have a reduction in synchronous firing for speech encoding and poor temporal resolution abilities. Since significant effect of aging on auditory temporal processing can be seen as earliest as in the middle aged group, the clinical population of diabetes mellitus type 2 have an increased susceptibility to these deficits. Considering diabetes is one of the common metabolic disorder in the middle aged Indian population, the findings of the present study can have significant clinical implication. Before implementing the above finding, further investigations to be validated on large sample. Speech evoked ABR can be a promised tool to assess the neural encoding of diabetes mellitus and other metabolic diseases.

6.1. Clinical Implications

- Speech evoked ABR can be used as a clinical non-invasive tool to tap the brainstem neuropathy in individuals with diabetes mellitus and can be used as a supplemental tool to click evoked ABR.
- Speech encoding in individuals with diabetes mellitus need to be a research focus.
- Temporal resolution difficulty in individuals with diabetes mellitus demonstrated through GDT and TMTF have significant clinical significance as it may adversely affect the speech perception.

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