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THE EFFECT OF DIABETES ON MEASURES OF AUDITION AND COGNITION AMONG VETERANS

by

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THESIS APPROVAL PAGE

This is to certify that the thesis prepared by Nicholas Reed entitled "The Effect of Diabetes on Measures of Audition and Cognition among Veterans" has been approved by the thesis committee as satisfactorily completing the thesis requirement for the degree of Doctor of Audiology.

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ABSTRACT

THE EFFECT OF DIABETES ON MEASURES OF AUDITION

AND COGNITION AMONG VETERANS

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Type 2 Diabetes Mellitus (DM) is a metabolic disease with complications that can impair auditory and cognitive function. This thesis describes cognitive function based on two cognitive behavioral measures (Digit Symbol Substitution [DSS] and Letter Number Sequencing subtests of the WAIS-III) and the electrophysiological P300 event-related potential and audiometric function based on pure-tone thresholds (0.25kHz threshold and pure-tone averages developed for low/mid- [0.5, 1, 2kHz], high- [3, 4, 6, 8kHz] and ultra-high frequencies [10, 12.5, 14kHz]), speech understanding (QuickSIN and time-compressed speech). Groups were constructed based on indices related to glycated hemoglobin (HbA1c) levels (control, prediabetic, all DM), or whether insulin was required to manage the DM (control, non-insulin-dependent [NIDDM], insulin-dependent [IDDM]). Following initial univariate statistical analyses, separate generalized linear regression models were fit to response measures. After adjusting for age, elevated pure-tone thresholds at 250Hz and low/mid-frequency PTA were associated with IDDM. Among diabetics, poorer thresholds were observed in IDDM compared with NIDDM groups. Additionally, IDDM group had, on average, the poorest cognitive and audiometric measures across groups. Overall results indicate DM-induced changes in cognition and audition, trending towards statistical significance, and generally associate better DM control with better outcome measures. Notably, effect sizes were small and speech frequencies were, on average, clinically normal in our cohort; therefore, not surprisingly, speech understanding was not significantly affected. This is the baseline report of a longitudinal study.

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KEY TO ABBREVIATIONS

ABR: Auditory Brainstem Response

ADA: American Diabetes Association

AGE: Advanced Glycation End Product

ANOVA: Analysis of Variance

ANSI: American National Standards Institute

BDI: Beck Depression Inventory

CDC: Centers for Disease Control and Prevention

CPRS: Computerized Patient Record System

DM: Diabetes Mellitus

DPOAE: Distortion-Product Otoacoustic Emission

DSS: Digit Symbol Substitution

ERP: Event-Related Potential

GLM: Generalized Linear Model

HbA1c: Glycated Hemoglobin

HDL: High-Density Lipoprotein

HINT: Hearing-in-Noise-test

IDDM: Insulin Dependent Diabetes Mellitus

IEEE: Institute of Electrical and Electronic Engineers

IRB: Institutional Review Board

LNS: Letter Number Sequencing

MMSE: Mini Mental State Exam

MRI: Magnetic Resonance Imaging

NCRAR: National Center for Rehabilitative Auditory Research

NHANES: National Health and Nutrition Examination Survey

NIDDM: Non-Insulin Dependent Diabetes Mellitus

NIH: National Institutes of Health

OAE: Otoacoustic Emission

PTA: Pure-Tone Average

PVAMC: Portland Veterans Affairs Medical Center

SRT: Speech Reception Threshold

TBI: Traumatic Brain Injury

TCS 50%: 50% Time-Compressed Speech

TCS 60%: 60% Time-Compressed Speech

TEOAE: Transient-Evoked Otoacoustic Emission

VA: Veterans Affairs

WHO: World Health Organization

WAIS-III: Wechsler Adult Intelligence Scale III

CHAPTER 1: INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that affects millions of Americans and is projected to affect exponentially more over the next several decades. The auditory system is not immune to the pathologic mechanisms of DM; the negative effects of DM on the auditory system have been observed at multiple levels from the peripheral to the cortical processes. These negative effects result in diminished ability to perceive sound and may interfere with interpretation of auditory information such as speech. Understanding speech involves processes that begin in the peripheral auditory system and brainstem with analysis of the acoustic components of the speech signal and proceed through semantic and syntactic analyses involving cortical neural functions. Deficits at any stage of processing may be reflected in poorer perception of speech, especially in adverse listening conditions. Based on the literature, it is likely that DM affects peripheral auditory function; however, the role of the severity of the disease and the extent of the impact on other levels of the auditory system is unclear. DM appears to have subtle effects on central auditory function, and deficits in higher-level cognitive impairment have also been documented in diabetics using both neurocognitive and electrophysiological methods. Previous studies have demonstrated that in individuals with hearing loss, cognitive deficits exacerbate difficulty with speech understanding (Lunner & Sundewall-Thoren, 2007). Thus in diabetics, hearing impairment and cognitive decline may interact and result in a substantial communication deficit. Furthermore, decline in any cognitive system, even a mild cognitive change, can be a risk factor for the development of more severe cognitive issues such as dementia and Alzheimer's, both of which have been documented in elevated levels among diabetics (Allen, Frier, & Strachan, 2004). Clearly, there is a need for research that will more clearly delineate the effects of DM and the influence of DM severity on

cognition, particularly for cognitive processing within the auditory cortex. Understanding the effects of DM on cognition and auditory processing is a first step toward potentially using DM interventions to reduce communication difficulties experienced by diabetics. The aims of this thesis are to determine whether Veterans with type 2 DM demonstrate impaired auditory or cognitive function compared to Veterans without Type 2 DM.

CHAPTER 2: LITERATURE REVIEW

Diabetes Mellitus

Diabetes overview. DM is a group of metabolic diseases characterized by hyperglycemia or higher than normal levels of blood glucose as a result of dysfunction in insulin secretion, insulin action or both (American Diabetes Association [ADA], 2011). DM is divided into two broad etiopathogenetic categories: type 1 and type 2. In type 1 DM, juvenile diabetes, the increase in blood glucose levels is a result of the body's immune system attacking the pancreas, which causes an inability to make the insulin hormone, which regulates blood glucose. Conversely, type 2 DM, formerly referred to as adult onset diabetes, is a result of a combination of the body's improper use of insulin and inadequate insulin secretion response. Type 2 DM is significantly more prevalent than type 1, affecting 90 to 95% of all cases (ADA, 2011; Centers for Disease Control and Prevention [CDC], 2011). Recently, another label associated with DM has emerged in the literature; prediabetes is a condition in which blood glucose levels are higher than average and approaching diabetic levels but not yet sufficient for diagnosis of the disease. Individuals with prediabetic blood glucose levels are prone to developing type 2 DM (ADA, 2011; Nichols, Hillier, & Brown, 2007). Glycated Hemoglobin (HbAlc), the ratio of glycated hemoglobin in relation to total hemoglobin, is a preferred method for measuring and monitoring blood glucose levels over the last 2-3 months and should be between 4.0-6.0% in non-diabetics (ADA, 2011).

Prevalence of diabetes. The Centers for Disease Control and Prevention (CDC) estimates that DM, diagnosed and undiagnosed, affected 25.8 million people in the United States as of 2010, and the World Health Organization (WHO) anticipates this number will increase to over 30 million people by 2030 (CDC, 2011; World Health Organization [WHO], 2013; Wild,

Roglic, Green, Sicree, & King, 2004). Moreover, the CDC reports an estimated 79 million Americans are prediabeticic (CDC, 2011). The high prevalence of DM is not limited to the population of the United States. A recent meta-analysis of literature and publications of major health organizations such as WHO and the American Diabetes Association (ADA) estimate that nations such as China and India will have approximately 62 and 87 million persons aged 20-79 with DM by 2030, respectively (Shaw, Sicree, & Zimmet, 2010). The prevalence of DM is higher among Veterans compared to the general American public due, in part, to the older age of the average Veteran. Approximately 1 in 5 Veterans have DM. This is mostly limited to type 2 DM as type 1 DM is generally considered an exclusionary factor to military service; however, there are cases of type 1 DM onset after beginning service in the military (Gale, 2002; Miller, Safford, & Pogach, 2004).

Physiological effects of diabetes mellitus. DM is characterized by the body's inability to regulate glucose in the bloodstream primarily due to the inability to produce or process insulin. Blood glucose levels can vary widely in individuals with DM, with elevated levels (hyperglycemia) immediately following the intake of carbohydrates and dangerously low levels after periods without food (hypoglycemia). Short-term hypoglycemia can result in light-headedness, loss of consciousness, and mild, momentary mental deficiencies. However, chronic hypoglycemia can result in severe cognitive and neurologic deficits. For diabetics receiving pharmacological or insulin treatment, hypoglycemia may be caused by artificially introducing too much insulin and over-regulating glucose, resulting in low blood sugar (ADA, 2011; Fowler, 2011; Kodl & Seaquist, 2008; Sommerfield, Deary, McAulay, & Frier, 2003; Strachan, Ewing, Frier, McCrimmon, & Deary, 2003). Acute hyperglycemia does not pose an immediate threat. Yet chronic hyperglycemia causes a myriad of symptoms in the body's renal, retinal, and

cardiovascular systems due to oxidative stress, micro- and macro-vascular abnormalities and neuropathic changes in affected individuals. The long-term complications of hyperglycemia are numerous and include retinopathy, nephropathy, peripheral neuropathy, autonomic neuropathy, neurodegeneration, atherosclerosis, cerebral ischemia, stroke, mild cognitive dysfunction and dementia (ADA, 2011; Fowler, 2011; Kodl & Seaquist, 2008; Strachan et al., 2003). More recently added to this list of complications is auditory dysfunction (Austin, Dille, Hungerford, Reed, & Konrad-Martin, 2013; Fowler & Jones, 1999; Frisina, Mapes, Kim, Frisina & Frisina, 2006; Maia & de Campos, 2005; Nathan et al., 2009). Interestingly, in prediabetes, pathologic and functional changes in tissues may be occurring without any overt clinical symptoms (ADA, 2011; Nichols et al., 2007).

Mechanisms of auditory dysfunction in diabetes. The exact pathogenesis of DM-related hearing and cognitive decline is still debated. In fact, some have speculated that the controversy among the association of hearing loss and DM stems from the currently unknown specific pathogenesis of hearing loss among diabetics and, thereby, an inability to establish a definitive causal relationship (Maia & de Campos, 2005; Wolfe, Honaker, & Decker, 2011). The location of the inner ear, a lack of human histological studies, and overall poor methodology of previous studies including lack of longitudinal studies, poor group control, and poor variable control, make it difficult to come to a conclusion regarding hearing loss and DM (Hirose, 1998; Maia & de Campos, 2005). In addition, hearing loss in diabetics may easily be mistaken for presbycusis due, in part, to the fact that many diabetics are older (ADA, 2011; Frisina et al. 2006; Hirose, 1998; Maia & de Campos, 2005). Nonetheless, researchers are in agreement that several of the mechanisms responsible for various other complications of DM may be plausible explanations for hearing loss among the diabetic population; oxidative stress, cellular

irregularities, homeostatic breakdowns, angiopathic complications (both micro- and macro-vascular), neural degeneration, and genetic abnormalities may all play an independent or synergistic role in causing hearing loss among diabetics (Fowler & Jones, 1999; Frisina et al., 2006; Fukushima et al., 2006; Maia & de Campos, 2005).

Higher oxidative stress levels have been established in diabetics versus non-diabetics (Aladag, Eyibilen, Güven, Atış, & Erkokmaz, 2009). Oxidative stress, often characterized by advanced glycation end products and reactive oxygen species, can induce inflammatory and thrombogenic reactions in the vascular system of the inner ear. This could result in hypoxia of the stria vascularis, altering the chemical homeostasis of the inner ear fluid, or in a thickening of the basement membranes (Fukushima et al., 2006;Yamagishi et al., 2012). While only speculation, homeostatic changes have been suggested as a pathogenesis of peripheral hearing loss among diabetics (Frisina et al., 2006; Hirose, 1998). Furthermore, oxidative stress damage is not limited to the microvascular complications in the inner ear mentioned above; it is also related to more global hypertension and various macrovascular complications which could lead to ischemia or stroke affecting the auditory cortex (Grossman, 2008; Kodl & Seaquist, 2008; Yamagishi et al., 2012). Furthermore, Lisowska, Namyslowski, Morawski, & Strojek (2001b) suggested oxidative stress could prove toxic to the inner ear independent of inducing vascular changes. Similarly, Dalton, Cruickshanks, Klein, Klein and Wiley (1998) suggested the nephrotoxic agents responsible for nephropathy among diabetics could have an ototoxic effect on the peripheral auditory system.

While Maia and de Campos (2005) noted that it is difficult to determine the etiology of hearing loss in diabetics due to difficulty in accessing histological assessments in humans and issues in studying homeostasis of the inner ear due to its location, microvascular anomalies

among diabetics have been documented in human cadaver studies. Wackym and Linthicum (1986) revealed thickened capillaries near the stria vascularis, thickened basilar membranes, and evidence of microvascular involvement near the endolymphatic sac among the temporal bones of 8 diabetics versus a control group of 10 healthy cadavers. By reviewing the medical history of the cadavers, they were able to associate patients with hearing loss with microvascular complications of the enolymphatic sac and a loss of hair cells among subjects with thickened basilar membranes. Similarly, Fukushima et al. (2006) found a loss of outer hair cells and microvascular complications of the stria vascularis in the temporal bones of type 2 diabetic cadavers compared to a control group of healthy cadavers. Interestingly, Makishima and Tanaka (1971) reported atrophy of the spiral ganglion neurons and general demyelization of the auditory nerve in 4 diabetic subjects.

Moreover, several studies were able to find correlations among hearing loss and various known microvascular complications (i.e. retinopathy or peripheral neuropathy) among diabetic populations. Bainbridge, Hoffman, and Cowie (2011) found a strong association between peripheral neuropathy and high frequency hearing loss. Dalton et al. (1998) saw an association between nephropathy and hearing loss while Weng, Chen, Hsu, and Tseng (2005) reported a statistically significant association between increased levels of serum albumin, an indicator of microvascular complications, and pure-tone hearing loss. Kurt et al. (2002) established that hearing loss was more prevalent among diabetics with retinopathy than those without and that hearing thresholds correlated with the degree of retinopathy. This relationship also correlated with severity of disease, as more advanced proliferative retinopathy was associated with worsened pure-tone thresholds. However, it should also be noted that some studies were unable to link any microvascular variables with tests of peripheral hearing loss (Vaughan, James,

McDermott, Griest, & Fausti, 2007). To that extent, Lisowska, et al. (2001b) were not able to establish a link between hearing loss in diabetics and microangiopathy, and suggested that a different pathogenesis was responsible for hearing loss.

Several studies have associated macrovascular complications with dysfunction of the peripheral auditory system. In a follow up to their 2008 study, Bainbridge et al. (2011) examined the data of the DM group (n=536) to identify risk factors for hearing impairment among diabetic adults. The researchers found that diabetics with macrovascular-related complications, including low high-density lipoprotein (HDL) cholesterol and a history of coronary heart disease, had a statistically significant higher likelihood of hearing impairment. Similarly, Gates, Cobb, D'Agostino, and Wolf (1993) reported an association between low HDL cholesterol and mid-frequency hearing loss among diabetics. In addition, Aimoni et al (2009) found a link between hearing loss and cardiovascular risk factors among diabetics.

Mechanisms for cognitive dysfunction in diabetes. Similar to the mechanistic effects of DM on the peripheral auditory system, several comparable potential mechanisms may affect the auditory cortex. It is likely the synergistic effect of these mechanisms that contributes to cognitive dysfunction. Macrovascular, microvascular, oxidative stress, and homeostatic insulin changes may all contribute to a cortical and neuronal breakdown (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Kodl & Seaquist, 2008). It is difficult to establish the specific pathogenesis for the same reasons mentioned above. Interestingly, multiple recent papers have speculated that the cortical changes documented within diabetic patients closely resembles the aging processes within normal elderly subjects. This has led to the speculation that DM may not induce changes as much as accelerate changes (Biessels et al., 2006; Kodl & Seaquist, 2008).

Type 1 and type 2 DM have been long connected with micro- and macrovascular changes throughout the body, and the brain is no exception (Biessels et al., 2006; Kodl & Seaquist, 2008). Researchers have found that diabetic brains have thickened basement membranes, a noted and common effect of microvascular complications (Biessels et al., 2006; Gispen & Biessels, 2000; Yamagishi et al., 2012). These microvascular changes may cause atrophy of white matter and other brain structures secondary to hypoxia, demyelination of cranial nerves and the spinal cord, and abnormal processing capabilities of structures with reduced blood flow (Gold et al., 2005; Gold et al., 2007; Kodl & Seaquist, 2008). Moreover, these factors may contribute to the increased rate of ischemic stroke among diabetics (Biessels et al., 2006).

It was once thought that the brain was an insulin-independent organ; however, recent findings have made it evident that varied insulin and glucose levels affect cerebral metabolism (Biessels et al., 2006; Kodl & Seaquist, 2008). Type 2 DM has been linked to hyperinsulinaemia, which is a risk factor for cognitive decline and dementia (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995; Luchsinger, Tang, Shea, & Mayeux, 2004). In addition, it has been established that insulin is transported across the blood-brain barrier and that there are insulin receptors throughout the brain, especially in the hippocampus and the cortex (Banks, 2004; Bondy & Cheng, 2004). Moreover, aging and Alzheimer's have been associated with insulin and insulin receptor changes in the brain (Frolich et al. 1998). Hemostatic alterations in insulin and glucose may also affect amyloid metabolism and contribute to oxidative stress levels.

It is believed that hyperglycemia alters function through a variety of biochemical mechanisms, including increased flux of glucose through the polyol and hexosamine pathways, and increased formation of advanced glycation end products (AGEs), diacylglycerol protein kinase C and reactive oxygen species. These toxic effects can lead to functional and structural

abnormalities within the brain by affecting brain tissue directly, causing impairments in neural transmission and synaptic plasticity, and by contributing to the widespread microvascular changes discussed above (Biessels et al., 1996; Biessels et al, 2006; Gispen & Biessels, 2000; Gold et al. 2005). Toth et al. (2006) demonstrated increased expression of AGEs and their receptors in the neurons and glial cells that contributed to white matter as well as myelin damage in diabetic mice. Post-mortem autopsy studies of humans have similarly revealed higher levels of oxidative stress (Girones et al., 2004).

Treatment and management. The severity of the complications of DM makes disease management crucial. Monitoring is vital to any DM management program. It is recommended that subjects engage in regular glucose monitoring and get regular (every 6 months) laboratory checks of their HbAlc levels. Diet, exercise, pharmacological agents, and insulin treatments are all regularly prescribed aspects of management programs for diabetics. Medications and insulin treatments require extra management as they can result in hypoglycemic states (Desouza, Bolli, & Fonseca, 2010). The terms insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) are used to describe diabetics who control their disease with insulin. Insulin dependence has been used in past studies as a measurement of severity of disease (Austin et al., 2009). In India, there has even been interest in using yoga and other holistic techniques to relieve stress in diabetics and, in theory, modulate the limbic system affecting endocrine secretions (Kyizom, Singh, Tandon, & Kumar, 2010).

Influence of Diabetes on Functional Measures of Audition

Throughout the last century, debates have continued over whether DM influences auditory system function. Contemporary studies in humans using physiological measures such as otoacoustic emissions (OAEs) and electrophysiological responses arising from the auditory nerve

and brainstem (auditory brainstem responses, ABRs) and from the cortex (cortical and event-related potentials, ERPs) suggest that DM may affect all levels of the auditory system. Nonetheless, the best evidence for the connection between DM and auditory dysfunction has been found among the numerous cross-sectional studies examining pure-tone audiometric function of diabetics and non-diabetics.

Pure-tone thresholds. Jordao (1857) is generally accepted as the first to report a case study of documented hearing loss secondary to DM. Since that report, numerous researchers have studied the relationship between DM and the auditory system to various conclusions.

Clinical studies. Gates et al. (1993) explored the relationship between cardiovascular risk factors, including DM, and hearing loss among 1662 elderly men and women. They defined hearing loss as low- (250, 500, and 1000 Hz) and high- (4000, 6000, and 8000 Hz) frequency pure-tone averages of ≥ 40 dB. The authors concluded that there was no general association between hearing loss and DM, despite finding an association between low-frequency hearing loss and blood glucose levels in women whereas higher blood glucose levels indicated poorer hearing loss ($p \leq .001$), as they found no other statistically significant association between hearing loss as indicated by pure-tones and DM using age-adjusted multivariate logistical regression models.

In a study aimed mainly at comparing the auditory brainstem response (ABR) among groups of diabetics, which will be further discussed in the ABR section of this literature review, Bayazit, Yilmaz, Kepekci, Mumbuc, and Kanlikama (2000) also reported elevated group mean pure-tone averages, indicating mild hearing loss, among a group of diabetics with microvascular complications (n=59) and a group without said complications (n=20). However, age was not addressed in this study.

In a cross-sectional study of 75 subjects with type 2 DM (mean age = 58.3 ± 12.9 years) and an age- and sex- matched control group of 45 subjects without DM, Kurt et al. (2002) found elevated pure-tone thresholds compared to the control group ($p<.001$) at all frequencies (250-8000 Hz). They excluded subjects with current or past ear disease, noise exposure, ototoxic drug usage, head trauma, or a family history of deafness. This study also found that poorly controlled DM (HbAlc ≥ 8%), severity of retinopathy, and duration of disease were significant factors associated with elevated hearing thresholds.

Diaz de Leon-Morales, Jauregui-Renaud, Garay-Sevilla, Hernandez-Prado and Malacara-Hernandez (2005) explored auditory function among 94 patients with type 2 DM (age=50±6 years) and 94 age- and sex-matched healthy subjects (age = 50 ± 6 years). The study excluded subjects with a history of ototoxic medication, unsafe noise exposure, or otological, central nervous system or cardiovascular disease. Pure-tone audiometry revealed a significant ($p<0.01$) difference only at 8000 Hz. Interestingly, speech audiometry results were mostly consistent with pure-tone audiometry except significantly ($p<0.05$) increased thresholds to discriminate at least 90% of monosyllabic stimuli were reported among diabetics.

Frisina, Mapes, Kim, Frisina and Frisina (2006) explored the auditory characteristics of type 2 DM by comparing the audiometric results of 30 type 2 diabetics (mean age=73 years) to a healthy age- and sex-matched control group (n=30). Pure-tone testing was conducted from 250-14000 Hz, in addition to tympanometry and speech audiometry. The researchers found that diabetics consistently had higher pure-tone thresholds than non-diabetics, most notably in low frequencies (500, 1000, 2000 Hz). In addition, diabetics demonstrated increased speech reception thresholds (SRT) compared to non-diabetics. Their results also demonstrated continuously higher thresholds in the right ear compared to the left ear within the diabetic group.

In a cross-sectional analysis of Veterans, Vaughan, James, McDermott, Griest, and Fausti (2007) compared the audiometric data of 342 subjects with DM and 352 subjects of normal health. The age range across both groups was 25-83 years. Pure-tone audiometry was tested from 250-16000 Hz. When age and noise exposure were controlled for, their study showed an overall trend of poorer hearing among diabetics versus non-diabetics. This difference was more pronounced in a younger group (diabetics > 60 years). Across all diabetic age groups, thresholds were elevated in high frequency pure-tone testing (8000-16000 Hz). They noted that these results may suggest that DM speeds the aging process, relating to early presbycusis, and that this conclusion should be further explored.

In another cross-sectional study of Veterans, Austin et al. (2009) found different associations between DM and hearing loss among various age groups. They classified their participants by insulin dependence: NIDDM (n = 88), IDDM (n = 77) and no DM (n = 137), and by age: 26-49 (n = 115), 50-56 (n = 95), and 57-71(n =92) years. While several audiometric measures were recorded, this article reported on pure-tone thresholds obtained from 250-14000 Hz. Their results revealed significantly elevated hearing thresholds at all frequencies for the NIDDM subjects and at 250-1000 Hz and 10,000-14,000 Hz for IDDM subjects within the 26-49 year age bracket. At the older ages, differential effects of DM on pure-tone thresholds were found only for IDDM subjects at select frequencies.

Epidemiological studies. Several large-scale epidemiological studies regarding the results of major national health surveys have found some degree of association between DM and hearing loss. These large-scale studies further support the association between auditory dysfunction and DM.

Bainbridge, Hoffman, and Cowie (2008) conducted a large, cross-sectional analysis of nationally representative data to determine whether hearing loss was more prevalent among U.S. adults with DM versus those without DM. A sample size of 5140 adults aged 20 to 69 years was obtained between the years 1999 and 2004 from the National Health and Nutrition Examination Survey (NHANES) by the National Center for Health Statistics. Among other measures, participants in the survey completed an audiometric examination by trained technicians with calibrated equipment, a DM questionnaire and a randomized assigned fasting protocol and subsequent blood draw (n=2259). Five hundred and thirty-six participants were identified as having DM. The researchers described hearing loss by a low/mid frequency (500, 1000, and 2000 Hz) and a high frequency (3000, 4000, 6000, and 8000 Hz) pure-tone average (PTA). A multivariate analysis adjusting for otologic concerns such as noise exposure, ototoxic medication, and demographic variables such as age, sex, ethnicity, socioeconomic status, and military history revealed diabetic subjects were 1.64 times as likely to have a low frequency PTA hearing loss in the better ear and 3.21 times as likely to have a high frequency PTA hearing loss in the better ear compared with non-diabetic individuals aged 20-69 years. Hirose (1998) noted that that the most significant finding in this study was the strong association between hearing loss and DM in a relatively younger age group, whereby other etiologies of hearing loss would be more uncommon (Hirose, 1998).

Dalton et al. (1998) explored the association of DM and hearing loss among a population of a Wisconsin town. Participants completed a comprehensive audiometric examination, including pure-tone audiometry at 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz, and a comprehensive medical history questionnaire. Subjects with incomplete data, questionable DM, or assumed type 1 DM (based on age of diagnosis) were excluded from the study, leaving 3373

participants and 344 type 2 diabetics. Hearing loss was defined as pure-tone averages (500-4000 Hz) >25 dB. Initial age-adjusted regression analysis revealed no statistically significant differences in hearing; however, when the study population was reanalyzed with participants with a history of ear surgery, unilateral hearing loss, and conductive hearing loss removed from the data set, there was a statistically significant association between DM and hearing loss (odds ratio = 1.41, 95% CI 1.05-1.88).

Agrawal, Platz, and Niparko (2009) evaluated the synergistic relationship of several cardiovascular risk factors, including DM, and noise exposure on frequency-specific audiometric thresholds using the NHANES data from 1999 to 2002. The study population (N= 3527) was limited to those aged 20 to 69 years that participated in the audiometric evaluation (air-conduction thresholds from 500 to 8000 Hz) and excluded those with unreliable audiometric data based on 1000 Hz test-retest thresholds. They defined hearing loss as a pure-tone average of $\geq$ 25 dB at 500, 1000, 2000 and 4000 Hz in each ear. Using multiple logistic regression models that controlled for other factors, the 321 adults with self-reported, physician-diagnosed DM were more likely to have hearing loss than those without DM (odds ratio = 2.0). Moreover, when the researchers evaluated hearing loss at specific frequencies they found diabetics had statistically significant ($p < 0.01$) worse hearing thresholds at lower (500 and 1000 Hz) and higher (3000, 4000, and 6000 Hz) frequencies compared to non-diabetic individuals. The researchers also found a significant interaction between DM, firearm noise exposure, and hearing loss at 3000 Hz. Interestingly, this same research group also looked at the NHANES data from 1999-2004 and found increased age-adjusted odds of vestibular dysfunction among diabetics with a higher HbA1c (odds ratio = 1.6) and longer duration (>10 years) of DM exposure (odds ratio = 2.0) (Agrawal, Carey, Della Santina, Schubert, & Minor 2009).

Ma, Gomez-Marin, Lee, and Balkany (1998) analyzed the results from 1740 participants who underwent audiometric evaluations (500, 1000, 2000, and 4000 Hz) and self-reported diabetic status from a national health survey of Hispanic-Americans. Initially, the researchers found statistically significant ($p < .05$) differences among diabetics and non-diabetics at all frequencies; however, this difference disappeared at all but 500 Hz when age-adjusted linear regression analysis was performed.

Overall, most studies have suggested that there is an association between DM and peripheral auditory dysfunction (e.g. Bainbridge, Hoffman, & Cowie, 2008; Frisina et al., 2006; Kurt et al., 2002; Lisowska 2001b). Moreover, several recent large reviews of relevant literature have similarly concluded that there is, in fact, a definitive association between hearing loss and DM and note that several studies with negative findings appear to be poorly designed, yet the specific etiologic effects on the auditory system remain speculation at this point (Austin et al., 2013; Fowler & Jones, 1999; Maia & de Campos, 2005; Wolfe et al., 2011).

Otoacoustic emissions. Results in the literature regarding OAEs in diabetics seem to be highly variable and many studies do not discuss their methods in great detail. Nonetheless, abnormal OAEs among diabetics are more frequently reported, which is suggestive of peripheral auditory dysfunction. Lisowska, Namyslowski, Morawski, and Strojek (2001a) and Frisina et al. (2006) found distortion product otoacoustic emissions (DPOAEs) were significantly reduced in amplitude among groups of 42 and 30 diabetics compared to age- and sex-matched controls. Ottaviani, Dozio, Neglia, Riccio, and Scavini (2002) found significantly ($p<0.001$) reduced transient evoked otoacoustic emissions (TEOAEs) and DPOAE mean intensities among 60 diabetics (mean age=31±6.23 years) compared with 58 age- and sex-matched controls. However, Erdem, Ozturan, Cem Miman, Ozturk, and Karatas (2003) found statistically different

amplitudes only at 4000 Hz using DPOAE testing when evaluating TEOAE and DPOAE results among 21 NIDDM subjects compared to an age- and sex-matched healthy control group (n=22). In addition, several studies have reported further reductions in OAEs among diabetics with evident microangiopathy versus diabetics without it (Lisowska et al., 2001a; Simoncelli et al., 1993).

Auditory brainstem response. Numerous researchers have examined the effect of DM on the ABR test and many studies revealed abnormal ABRs among diabetics, even when hearing loss was accounted for. Delays in central conduction time have led researchers to suggest that the effects of DM may affect central processes more than peripheral auditory functions (Huang, Lu, Chang, Tsai & Chang, 2010; Lisowska et al., 2001a). Lisowska et al (2001a) revealed significantly longer ABR latencies for waves I, III, and V and increased I to V interpeak latencies among a diabetic group versus a control group. Similarly, Al-Azzawi and Mirza (2004) and Diaz de Leon-Morales et al. (2005) reported significant increases in absolute latencies, interpeak latencies, and wave V amplitudes among diabetics compared to healthy age- and sex-matched controls. Durmus, Yetiser, and Durmus (2004) also found significantly ($p < 0.05$) prolonged absolute wave latencies (I, III, & V) and interpeak latencies (I-III, III-V, & I-V) among the diabetic group versus controls. Interestingly, when they analyzed the data within the diabetic group, they revealed that absolute wave III and V latencies were prolonged in type 2 subjects versus type 1 subjects. Huang, Lu, Chang, Tsai and Chang (2010) reviewed the charts of all the patients who had ever completed a neurologic screening, which included an ABR, at a hospital in Taiwan. In a random selection of 43 diabetics and 43 age- and sex-matched healthy controls without complications that would otherwise influence the ABR, they found that the

diabetics had significantly prolonged interpeak latencies I-III and I-V. This difference was more pronounced among diabetics with documented peripheral neuropathy.

It seems that even within diabetic groups there is a difference in ABR measurements. Bayazit, Yilmaz, et al. (2000) compared the ABRs of 59 diabetic (both types) patients with complications related to DM (e.g. retinopathy, peripheral neuropathy) and 20 similar age- and sex- matched diabetics with no known complications of DM. ABRs revealed the group with complications had significantly ($p < 0.001$) longer absolute wave I, III, and V and interpeak I-III and I-V latencies compared to the diabetic group without complications. Wave V amplitude was also significantly reduced among this group ($p < 0.001$). In a similar study, Bayazit, Bekir, Güngör, Kepekçi, Mumbuç, & Kanlíkama (2000) found prolonged ABRs among diabetics with retinopathy versus diabetics without retinopathy. These results suggest that the microvascular complications underlying conditions such as retinopathy and peripheral neuropathy may play a role in a sort of brainstem neuropathy related to DM.

Some studies have also highlighted a significant asymmetric difference among ABRs (Diaz de Leon-Morales, Jauregui-Renaud, Garay-Sevilla, Hernandez-Prado and Malacara-Hernandez, 2005; Vaughan et al., 2007). An example of this can be found in Vaughan et al. (2007) who reported significant mean latency differences between diabetic and non-diabetic patients using regression models that adjusted for variables such as age, hearing loss, and various diabetic-related conditions when they reported on data obtained from 261 diabetic and 326 non-diabetic Veterans with measurable auditory brainstem responses (ABRs). The group found significant differences between subject groups, namely: prolonged ABR absolute latencies (III & V) in the right ear using condensation clicks, interpeak latencies (I-V, & I-III) in both the right and left ear using condensation clicks, and interpeak latencies (I-V, & III-V) in the left ear using

rarefaction clicks among the diabetic group. Notably, they also found a longer wave I threshold in the right ear using rarefaction clicks among the non-diabetics. Interestingly, this group's regression models revealed that age and hearing loss were significant factors in all the absolute latency conditions, and age was a factor in the interpeak latencies using condensation clicks in the right ear.

Overall it appears that the literature body regarding the ABR in diabetics is growing. There is an evident association between abnormal ABR measurements, especially neural conduction time, and DM; however, the overall nature of the relationship is still undefined. Some researchers have noted that abnormal ABR results appear to be more pronounced while measurements of cochlear receptor function seem to be more subtle, which has led them to theorize that perhaps the effect of DM is greater on the neural and cognitive levels of the auditory system rather than the cochlear peripheral level (Liskowsa et al., 2001a).

Measures of speech understanding. While it is evident that many studies have been conducted regarding measures of peripheral and central auditory function with tone-based stimuli, few studies have looked at speech understanding among subjects with DM. Speech understanding is affected by both peripheral auditory function and cognitive ability (Lunner & Sundewall-Thoren, 2007). Frisina et al. (2006) found subjects with type 2 DM have higher thresholds on the Hearing-in-Noise-Test (HINT) in both quiet ($p < 0.02$) and background noise conditions ($p < 0.0001$). They concluded it was likely the hyperglycemic effects of DM were contributing to both the peripheral and central auditory system. More information in this area is needed to understand the full extent of the impact DM has on the auditory system.

Influence of Diabetes on Functional Measures of Cognition

Large-scale clinical studies and meta-analyses. In a meta-analysis of 25 articles compromising a total population of 8,656 subjects, Cukierman, Gerstein, and Williamson (2005) concluded that diabetics were at a 1.5-fold greater risk for cognitive decline and a 1.6-fold greater risk of future dementia than non-diabetics. Stewart and Liolitsa (1999) found a trend in the literature of increased levels of Alzheimer's and dementia among diabetics within cross-sectional and population studies. Interestingly, they noted that it is likely that diabetics are often misdiagnosed with Alzheimer's, and that dementia may be the result of other etiologies. The prevalence of Alzheimer's was significantly increased among diabetics and even more so among insulin-treated diabetics in one population study (Ott et al., 1996). It is unknown whether DM induces or exacerbates the pathological process of abnormal cognitive function (Stewart & Liolitsa, 1999). Curb et al. (1999) linked DM to Alzheimer's through cerebrovascular diseases (i.e. a non-pathologically observed process like infarction or ischemia). Luchsinger et al. (2007) conducted a longitudinal study of 918 elderly adults. They found a significantly higher number of participants who reported DM to have mild cognitive impairment versus those who did not report having DM. Moreover, Roberts et al. (2008) reported that mild cognitive impairment was associated with earlier onset, longer duration and greater severity of DM. Despite the numerous studies, the physiological effect of DM on cognitive function has been understudied when compared to the retinal, renal, cardiovascular, and peripheral nervous systems (Kodl & Seaquist, 2008).

In a meta-analysis of literature, Brands, Biessels, De Haan, Kappelle, and Kessels (2005) reviewed 33 studies on neuropsychological function in type 1 diabetics and concluded available evidence strongly supported existence of a relationship between cognitive dysfunction and DM,

particularly in the domains of intelligence, speech of information processing, psychomotor efficiency, visual, and sustained attention. In another large-scale review of literature, Awad, Gagnon, and Messier (2004) noted that "more statistically significant differences between diabetic patients and controls were found for measures of immediate noncontextual verbal memory as well as on processing speed and cognitive screening measures…compared to other measures evaluated" (p. 1061).

Studies support the notion that glycemic control appears to play a role in the degree of cognitive dysfunction, especially among type 2 diabetics (Kodl & Seaquist, 2008). Acute changes in glucose levels have been demonstrated to significantly affect general auditory processing and temporal processing tasks (McCrimmon, Deary, & Frier, 1997). Studies have found that cognitive function significantly declines during acute hypoglycemic and hyperglycemic episodes, suggesting poor metabolic control results in poorer cognition (Sommerfield et al., 2003; Sommerfield, Deary, & Frier, 2004). Well-controlled and well-managed glucose levels seem to correlate with better cognitive function among diabetics, especially for type 2 diabetics (Kodl & Seaquist, 2008). Yaffe, Blackwell, Whitmer, Krueger, and Barret-Conner (2006) found HbA1c levels above 7.0% correlated with increased risk for mild cognitive dysfunction. Similarly, Reaven, Thompson, Nahum, and Haskins (1990) reported an inverse relationship between HbAlc and neurocognitive tests measuring learning and psychomotor performance in older patients with type 2 DM. Moreover, Munshi et al. (2006) reported similar results in that poorer scores on the MMSE correlated with poorer HbA1c levels in diabetics over the age of 70.

Cognitive behavioral tests. It has been consistently found that DM affects cognitive function (Brands, Biessels, De Haan, Kappelle, & Kessels, 2005; Kloppenborg, van den Berg,

Kappelle, & Biessels, 2008; Kodl & Seaquist, 2008; Roberts et al., 2008; Strachan, Deary, Ewing, & Frier 1997). Notably, a higher incidence of Alzheimer's disease and vascular dementia has also been found among diabetics (Cukierman, Gerstein & Williamson, 2005; Curb et al., 1999; Kodl & Seaquist, 2008; Leibson et al., 1997; Ott et al., 1996).

Mini mental mind status exam. The Mini Mental State Exam (MMSE) is a brief test designed to screen for general cognitive impairment mainly in the domains of language and memory. Its scale ranges from 0-26, with higher numbers indicating better performance (Folstein, Folstein, and McHugh, 1975; Gregg et al., 2000).

Several studies have found lower than normal scores on the MMSE in diabetic versus non-diabetic subjects (Gregg et al., 2000; Strachan et al., 1997). Interestingly, Vanhanen et al. (1998) found that even elderly subjects with impaired glucose tolerance, a milder abnormality of glucose metabolism than DM and comparable to prediabetes, scored lower on cognitive function tests, particularly the MMSE. Hiltunen, Keinanen-Kiukaanniemi, and Läärä (2001) found that subjects with previously undiagnosed DM preformed significantly poorer on the MMSE than those who had been previously diagnosed and were actively treating their illness.

Digit symbol substitution test. The Digit Symbol Subtest (DSS) of the Wechsler Adult Intelligence Scale III (WAIS-III) is a neuropsychological screening test from the WAIS-III that involves the timed translation of 9 numbers into their corresponding symbols using a key and is sensitive to dysfunction, primarily in processing speed and secondarily in memory (Wechsler, 1981; Joy, Kaplan, & Fein, 2004). In a meta-analysis of 25 articles compromising a population of 8,656 subjects, Cukierman et al. (2005) found in general, diabetics had a greater likelihood of being diagnosed with cognitive dysfunction. Specifically, they found the DSS to be the most common assessment associated with abnormal results, with odds ratios of 1.7.

Vanhanen et al. (1997) compared the neurological behavioral test battery results of 26 elderly subjects with confirmed DM against two groups: one with increased risk for developing type 2 DM (n=22) and one with low risk for developing type 2 DM (n=26). Risk was defined by the subject's glucose levels. Patients with confirmed type 2 DM and at high risk for developing type 2 DM displayed impairment on memory, attention, visuomotor speed, and verbal fluency tasks. Notably, these two groups both performed poorly on the DSS of the Wechsler Adult Intelligence Scale III (WAIS-III). Similarly, in a longitudinal study of 682 diabetic elderly women compared against a control of 8,997 age-matched non-diabetic women, Gregg et al. (2000) found lower baseline cognitive function in addition to a trend of increased cognitive decline as the duration of DM increased using a neurological behavioral test battery that included the DSS. Meneilly, Cheung, Tessier, Yakura, and Tuokko (1993) evaluated the performance of 16 elderly patients with type 2 DM on a neurologic exam that included the DSS at baseline, and at 1 and 6 months following treatment with Glipizide, a hypoglycemic agent. Their results suggested that cognition improves when glucose levels are well controlled. Fontbonne, Berr, Ducimetiere, and Alperovitch (2001) found DSS scores that were significantly lower in diabetics versus non-diabetics.

Strachan, Ewing, Frier, McCrimmon, & Deary (2003) looked at the effects of acute hypoglycemia on 15 adults with uncomplicated type 1 DM. Hypoglycemia was induced using a hyper insulinemic glucose clamp procedure. They found that scores on the DSS were significantly ($p<0.001$) reduced during hypoglycemia. Interestingly, they also found acute hypoglycemia correlated with deteriorated auditory temporal processing and verbal working memory tasks. This agreed with the group's earlier findings that several cognitive measures,

notably the DSS score, declined during hypoglycemic episodes in non-diabetics (McCrimmon et al. 1997).

Letter number sequencing. Another test of the WAIS-III is the Letter Number Sequencing (LNS) subtest, a test of auditory working memory and divided attention (Wechsler, 1981; Lin, Northam, Rankins, Werther, & Cameron, 2010). Some authors have noted that diabetics seem to have more difficulty in the verbal memory subcategory of cognition versus other domains (Ryan & Geckle, 2000b).

Lin and colleagues (2010) reported poorer scores on measurements of cognitive working memory in diabetics versus a normal control using the LNS subtest of the WAIS-III, a test of working memory task accuracy. Weinger et al. (2008) found that subjects with type 1 DM generally performed poorer than a non-diabetic control group ($p \leq 0.01$). Additionally, LNS subtest results have been reported as poorer during episodes of extreme acute glucose impairment (hypo- and hyper-glycemia) in patients with type 1 and type 2 DM (Sommerfield et al., 2003; Sommerfield et al., 2004).

Cortical evoked potentials. Late or cortical evoked potentials have been largely ignored in the literature regarding auditory-related dysfunction and diabetics. Cooray, Maurex, and Brismar (2008) measured auditory evoked potentials in 119 type 1 diabetics and compared them to 61 age- and sex-matched healthy controls. They found that the presence of DM had no effect on N1 latency but did result in a significant decrease in amplitude of N1. Interestingly, they found the decrease in N1 amplitude correlated significantly with tests of psychomotor function. Vanhanen et al. (1996) also found that the N1 was reduced in amplitude among the audiometric data of 342 subjects with DM compared with 352 subjects in normal health. One study found the slow cortical potentials were unaffected by acute hypoglycemia; however, the authors noted that

their conclusion should not infer that these potentials are immune from the long-term effects of hypoglycemia (Strachan et al., 2003).

P300. Electrophysiologic measures can be used to provide objective evidence of processing speed changes and control of attentional resource allocation (Arnell, 2006; Tays, Dywan, Mathewson, & Segalowitz, 2008). The auditory P300 is an endogenous evoked potential that represents the subject's ability to consciously recognize, classify, and discriminate stimuli (Coles & Rugg, 1995). Thus, the P300 can be used as a measure of working memory in an auditory discrimination paradigm (Dolu, Başar-Eroğlu, Özesmi, & Süer, 2005). Abnormalities in the auditory P300 potential in latency and amplitude among diabetic patients, suggesting a slowing in the speed of cognitive processing, have been documented in the literature (Alvarenga et al., 2005; Cooray, Maurex, & Brismar, 2008; Cosway, Strachan, Dougall, Frier, & Deary, 2001; Kurita, Mochio, & Isogai, 1995; Kyizom et al.,2010; Pozzessere et al.,1991; Strachan et al., 2003; Tandon, Verma, & Ram, 1999; Vanhanen et al., 1996).

Pozzessere et al. (1991) demonstrated statically significant ($P<0.001$) P300 wave latency changes among diabetic patients in a study of 16 IDDM patients when compared with age- and sex-matched non-diabetic subjects. A mean P300 latency value of 358.8 ms was obtained in the diabetic group versus a latency value of 320.9 ms in the control group. Similarly, Tandon, Verma, and Ram (1999) reported a statistically significant ($P<0.001$) increase in P300 latency among 30 type 2 diabetics versus a control group of 30 non-diabetic subjects matched for similar age, educational background, and socio-economic background. They reported a mean ± standard deviation P300 latency of 326.66 ms ± 26.4 among the control group versus 391.60 ms ± 49.7 in the diabetic group. N2b was also significantly delayed in this study. These findings were corroborated by Cooray et al. (2008), who reported a significant increase ($P<0.0004$) in P300

latency among diabetics compared to non-diabetics independent of age effects, and Kurita, Mochio, and Isogai (1995), who found increased P300 latencies and increased ABR interpeak latencies wave I-V among 40 NIDDM subjects versus 20 age-matched neurologically healthy volunteers. Lastly, Alvarenga et al. (2005) explored the P300 in 16 diabetic and 17 age-, sex-, and hearing loss-matched controls. Their analysis revealed a statistically significant increase in P300 latency among the diabetic group.

P300 amplitude measures have varied much more in the literature and differences are often insignificant between groups due to individual extremes. Nonetheless, Vanhanen et al. (1996) found decreased amplitudes using the late cortical potentials N100 and P300 in a smaller study (n=9) of elderly type 2 diabetics versus controls. Alvarenga et al. (2005) reported a general, though not significant, decrease in P300 amplitude among the diabetic group when measured from electrode Cz.

As noted above, glycemic levels often correlate with changes in cognition. This effect has varied in the P300 literature. When Alvarenga et al. (2005) analyzed data further within their diabetic cohort, they found that hypoglycemic levels of glucose correlated with increased latency and decreased amplitude of the P300. They suggested that use of the P300 in diabetic populations may prove an efficient procedure in preventing and monitoring neurologic complications of DM. However, Strachan et al. (2003) found that P300 latency and amplitude was unaffected by induced hypoglycemia among 15 type 1 diabetics. Geisler and Polich (1994) concluded that increased glucose levels via diet changes had no effect on the P300 in non-diabetic subjects.

A few studies have compared P300 results to other measures such as magnetic resonance imaging (MRI) and neurocognitive behavior tests and suggested that electrophysiological

measures are more sensitive to memory impairments than behavioral neurocognitive measurements. Some have even suggested that electrophysiological measurements, such as the P300, could be sensitive early indicators of higher level processing deficits. Kurita et al. (1995) conducted MRIs on 13 randomly selected diabetic patients; of these, 9 had normal MRI scans despite prolonged P300 latencies. In spite of these unremarkable and generally normal brain scans, electrophysiological results were significantly prolonged in these subjects, which led the authors to suggest this supports "the concept that metabolic derangement per se may play a role in the occurrence and progression of the central nervous system involvement in NIDDM" (p. 322). Cooray et al. (2008) compared the P300 to several cognitive processes and noted that it correlated with measurements of executive functions and the global cognitive dysfunction score. Cosway, Strachan, Dougall, Frier, and Deary (2001) reported no significant differences on any psychometric tests (16 total) or on latency or amplitude measures of the P300 between a group of 38 participants with uncomplicated and well-controlled type 2 DM and 38 age- and gender-matched healthy participants. They went to excruciating lengths to eliminate any participants with any known variables that might affect tests of cognition. Pozzessere et al. (1991) found no statistically significant correlation between P300 measures and behavioral neurological tests in either a diabetic or control group. Moreover, they saw statistically significant breakdowns in the P300 more often than neurobehavioral tests measuring short-term memory. They suggested that because the two measures did not correlate and because the P300 seemed to be abnormal more often than the neurobehavioral tests, the P300 may be a strong indicator of early changes to the higher cognitive functions and, when combined with short latency evoked potentials, could indicate early changes to neural conduction.

Specific Aims of This Research

As evidenced in the studies described above, there is a clear association between DM and hearing loss as well as between DM and cognition. Even though these deficits are likely to interact to degrade speech understanding among individuals with DM, no studies appear to have examined these outcomes contemporaneously, and researchers have not typically controlled for hearing loss when measuring cognitive function. Moreover, many of the current cross-sectional studies in the literature involving hearing or cognition are too small to be applied to the larger population and did not account for other variables that may affect outcomes, such as age. Finally, it is not yet clear whether disease severity strongly influences hearing and cognitive outcomes among individuals with DM. If DM-related deficits in auditory and cognitive function are associated with the severity of the disease then mechanisms to control disease severity may prevent or ameliorate communication problems in diabetics.

The proposed research has the following specific aims:

Specific aim 1. Determine whether Veterans with type 2 DM demonstrate greater deficits in the ability to process auditory and non-auditory stimuli at cognitive levels as compared to Veterans without DM. Hypothesis 1: We expect results that suggest poorer auditory and cognitive function among individuals with DM compared with those without DM. Impaired cognitive function may be more readily apparent using electrophysiologic measures (e.g. the P300) than compared with neurocognitive measures, such as the LNS and the DSS.

Specific aim 2. Determine whether Veterans with type 2 DM demonstrate impaired hearing compared to Veterans without DM, measured using pure-tone thresholds and speech understanding performance scores. Hypothesis 1: We expect results that suggest poorer auditory function among individuals with DM compared with those without DM.

CHAPTER 3: MATERIALS AND METHODS

This study is a cross-sectional sample derived from a larger, longitudinal research study on DM and hearing being conducted at the National Center for Rehabilitative Auditory Research (NCRAR) by Dawn Konrad-Martin, Ph.D. and Marilyn Dille, Ph.D. Other tests measured in addition to those reported in this thesis include: otoacoustic emissions, auditory brainstem response, and late cortical potentials. This study received approval from the Portland VA Medical Center (PVAMC) IRB committee.

Participants

Potential participants were identified from a previous study regarding DM and hearing loss conducted at the NCRAR, a center of excellence in the Veterans Affairs (VA) system located at the PVAMC in Portland, Oregon. Eligible Veterans from a previous study were those who entered that study at no more than 57 years old and had hearing thresholds less than 40 dB HL at 2 kHz and less than 70 dB HL at 4 kHz in at least one ear. Participants from previous studies who met the inclusion criteria were assigned random numbers and contacted using a random number system. In the case that a participant was contacted and was found to no longer meet the inclusion criteria, the next patient on the randomized list was contacted. Additionally, new potential participants were identified through a PVAMC diabetic registry and electronic medical records. Those who met the initial inclusion criteria, no more than 57 years old and met the same hearing threshold criteria described above if audiometric data were available, were assigned a random number and recruited in random order using a modified opt-out procedure. Letters were sent to potential participants and a phone interview was conducted for those interested in the study. The modified opt-out procedure entailed following up with potential participants who responded they were interested in the study and those who did not respond to

the letter at all while only refraining from contacting those who explicitly requested not to be contacted. Further, flyers were posted throughout the PVAMC to build interest in the study and Veterans who contacted the NCRAR with interest in the study were screened for exclusionary criteria.

Participants with active middle-ear pathologies, undergoing treatment for cancer, and/or with diagnosis of multiple sclerosis or other neurologic diseases were excluded from the study. In addition, those using medication that might impact assessment of auditory function or ability to perform experimental tasks (i.e. pharmacologically induced drowsiness or confusion) and/or those who were unable to complete the auditory assessment or experimental tasks due to language barriers or cognitive dysfunction such as dementia were excluded. Based on the above inclusion and exclusion criteria, 150 Veterans were eligible for enrollment in the study and were secondarily screened in the laboratory.

Screening. To verify eligibility for the study, pure-tone audiometry, immittance audiometry, and a MMSE were conducted. All participants were required to score at or above 24 to pass the MMSE in order to rule out major cognitive deficits. The MMSE was administered according to the test instructions (Folstein et al., 1975). Pure-tone air conduction thresholds were obtained at octave frequencies from 250 Hz through 4000 Hz and bone conduction thresholds were tested at 500, 1000, 2000 and 4000 Hz. In addition to bone conduction, immittance audiometry and otoscopy were used to assess middle ear function. Air bone gaps were defined as gaps $\geq$ 15 dB HL at a given frequency and normal tympanometry was defined as a compliance measure of .3-1.6 mL obtained between -100 to +50 daPa and less than or equal to 2.5 cc ear canal volume. Of the 150 eligible subjects, 144 subjects were enrolled. Four subjects were not

enrolled due to excessive hearing loss (n=4) and two subjects failed to show for the visit. No subjects failed the MMSE screening.

Data Collection

Data was collected at the NCRAR. All audiometric, speech recognition, and electrophysiological testing was conducted in a double-walled sound booth by licensed and trained research audiologists or by audiology graduate students under the supervision of said audiologists. Test sessions required approximately 6 hours with an hour long lunch break built into the schedule. Test order was at the discretion of the audiologist, with the electrophysiological data generally gathered at the end of the session. All participants consented to participate in the study following the guidelines of PVAMC's Institutional Review Board.

Questionnaires. A demographic questionnaire was administered as a written survey to gather information about the participants' hearing history, noise exposure history, medical history, occupational history, education level, and general history of DM including duration, treatment history, and complications. The Beck Depression Inventory (BDI) was administered orally by a licensed and trained research audiologist. Participants with high BDI scores were informed of such and offered help contacting the mental health clinic at the PVAMC. While participants were not excluded based on their BDI score, those taking medication that may interfere with experimental tasks were excluded as noted above.

Diabetic measures. Diabetic participants were required to have type 2 DM as diagnosed by a physician based on self-report and verified when possible using the VA's Computerized Patient Record System (CPRS) or the PVAMC electronic diabetic registry. HbA1c measures for diabetic participants were obtained from the PVAMC electronic medical records. In the case that the participant had not had an HbA1c measurement in the last 3 months

or was a non-diabetic participant, the HbA1c measure was obtained on the day of their visit to NCRAR. Trained research audiologists obtained a single drop of blood via finger stick method for analysis and used a Bayer DCA 2000+ Analyzer to obtain HbA1c measurement.

Tests of Hearing

Audiometric data. Pure-tone thresholds were obtained using the modified Hughson-Westlake procedure (Carhart & Jerger, 1959) on a GSI 61 Clinical Audiometer (Grason-Stradler, Inc., Madison, WI), calibrated at least annually to American National Standards Institute (ANSI) standards (ANSI S3.6, 2004), using Etymotic Research (ER3A) (Etymotic Research, Inc., Elk Grove Village, IL) insert earphones. Participants responded to stimuli by raising their hand when they heard the signal. Standard audiometric frequencies from 250-8000 Hz were tested as well as the interoctave frequencies 3000 and 6000 Hz and the extended high frequencies 10000, 12500 and 14000 Hz. Extended high frequencies were tested using Sennheiser HD-200 headphone (Sennheiser Electronic Corp., Old Lyme, CT). The maximum output for the extended high frequencies was 110 dB HL at 10000 and 12500 Hz and 95 dB HL at 14000 Hz.

Speech recognition tests. Recorded speech was delivered through a CD Player via GSI Clinical Audiometer (Grason-Stadler, Inc., Madison, WI) calibrated to ANSI standards (ANSI S3.6, 2004) with ER3A (Etymotic Research, Inc., Elk Grove Village, IL) insert earphones.

The QuickSIN (Etymotic Research, Inc.), a test of speech understanding in 4-talker babble background noise, was administered binaurally at 70 dB HL. During this test, tracks consisting of 6 sentences with increasingly difficult signal to background noise ratios were presented with instructions to repeat the sentence after the recording stopped. Sentences were scored and the signal to noise ratio loss for each track was calculated according to the QuickSIN manual (Etymotic Research, Inc). Participants were administered a practice track prior to actual

testing. The average score of 2 tracks was calculated as the final score. Final scores could range from -4.5 to 25.5, where -4.5 indicated a perfect score and 25.5 indicated 0 correct.

Time-compressed speech testing utilized the Institute of Electrical and Electronic Engineers (IEEE) sentences (Institute of Electrical and Electronic Engineers, 1969) which are both semantically and syntactically correct and contain 5 words minus prepositions such as 'the' and connecting words such as 'and.' Sentences were compressed with a custom software algorithm at rates of 50% and 60%. Testing was presented binaurally at 40 dB SL re: binaural high frequency PTA of right and left pure-tones thresholds at 2, 3, and 4 kHz. Participants were instructed to repeat the sentence presented to them and, immediately following repetition, rate their confidence in their response on a scale of one to three. One was equal to most confident and three was equal to least confident. Participants were first presented 10 sentences with no compression to acclimate to the task. Following this, they were presented a practice set of 5 sentences at a compression rate of 50% with feedback from the researcher of what words they missed when applicable and 5 more practice sentences at a compression rate of 50% with no feedback before being presented a final 10 sentences at a compression rate of 50% for actual scoring. This process was repeated with sentences compressed at a rate of 60%. Points were awarded based on the repetition of the 5 words in each sentence giving a total possible score of 50 (i.e. 5 words per a sentence and 10 sentences per test). Final scoring was based on the repeated percent correct with a possible score range of 0-100%.

Tests of Cognition

Behavioral measures. The DSS and LNS, two subtests of the WAIS-III, were utilized in this study. Please refer to the Wechsler-III manual (Wechsler, 1997) for specific testing instructions; however, a summary of the tests themselves will be presented here. These tasks

were completed sequentially, in no set order, in a quiet room at a comfortable conversation level for the participant.

The WAIS-III LNS subtest (Wechsler, 1997) is a test of auditory working memory and sequencing which was selected to assess the effect of DM on cognitive function and compare against the electrophysiological P300 response. A combination of letters and numbers was presented orally in a random order and the participant was instructed to repeat the numbers in ascending order first, followed by the letters in alphabetical order. For example, the presentation of K-6-B-3 would be correctly repeated 3-6-B-K. The test consists of 3 practice trials with immediate feedback from the researcher followed by 21 trials for scoring. One point was awarded for a correct response for a maximum possible score of 21.

The WAIS-III DSS (Wechsler, 1997) is a timed test of processing speed, working memory, and executive function which was also selected to assess the effect of DM on cognitive function and to compare against the P300. Participants were given a code key with a series of symbols that match and correspond to the numbers 1 through 9. Following this is a table of numbers 1 through 9 in random order. The participant was instructed to match the correct symbol to the number in order and as quickly as possible without making mistakes or skipping throughout the test (i.e. filling out all of the number 9 blocks in the table). Prior to beginning the actual task, the participant completed a practice task of matching 5 numbers to their corresponding symbols and reviewed it with the researcher. Following this practice run, the actual task commenced and was terminated after 120 seconds. One point was awarded for each correct symbol to number match for a total maximum score of 133 points.

Electrophysiologic measures. The P300 event-related potential (ERP) was recorded using the Neuroscan System (Compumedics Corp., Charlotte, N.C.). The Neuroscan electrode

cap (64 channel Quik Cap) was used to acquire analog electrical responses. Active electrodes included Fpz, Fz, Cz, Pz, F3, F4, C3, C4, P3, P4, P7, P8, T7 and T8 referenced to the tip of the nose and ground placed between Fz and Fpz. Additionally, electrodes were placed above and below the left eye and at the lateral canthus of each eye to detect horizontal and vertical eye movement. All electrode impedances were below 2000 ohms. The P300 was obtained with an oddball stimulus paradigm presented binaurally at 30 dB SL (re PTA of both ears at 500, 1000, and 2000 Hz). Pure-tone stimuli were presented with an occurrence of 80% for the standard stimuli (500 Hz) and 20% for the oddball or deviant stimuli (1000 Hz). 250 trials were collected for each individual waveform. Signals were bandpass filtered between DC-200 Hz with offline filtering of 0.15-200 Hz. Pz was the primary electrode used for scoring amplitude and latency while Fz, Cz, and Pz were used to demonstrate scalp distribution. Excessive eye movement and blinks were processed and removed offline. Scoring was completed by an automated system designed and programmed at the NCRAR and all initial output measurements were cross-checked by two researchers for accuracy. Any discrepancies found by the researchers were discussed with the entire research team. Amplitude of the P300 is defined as the voltage difference of the largest positive peak compared to the largest negative trough between 250-450 ms. The peak latency of the P300 is defined as the point in time at which the response reaches 50% of its area within the pre-established interval window within the 250-450 ms timeframe. Peaks were initially scored using a custom automated method. Peaks were checked and if needed, re-scored independently by two audiologists. Any disagreements between them were reconciled by a third audiologist.

Payment

Each participant was paid $10 for a screening visit to determine whether they met study criteria. Enrolled participants with DM were paid $90 per visit and those without DM were paid $70 per visit. Payment was reduced for non-diabetics because they did not need additional measures associated with DM.

Data Management and Quality Control

Pure-tone threshold data, DSS and LNS scores were manually entered into Microsoft Access and then converted into a file in SPSS version 21 for initial data cleaning, reduction and analysis. Automatic scoring of the P300 populated a database automatically so that the only data entered manually were those determined by the audiologists to have been incorrectly measured by the algorithm. This amounted to less than 10% of the data.

Missing data was cross checked with the participants' files to ensure a complete data set. If data was truly missing, it was treated as such in the analysis. In the event that no response was obtained for pure tones at the maximum output of the equipment, the recorded threshold was arbitrarily set to the maximum output of the equipment (110 dB HL). All questionnaires were scanned twice and discordant information was identified and corrected using the PVAMC patient database. Patient-reported data used in this study included patient age, patient gender, year of onset of DM, type of DM, and insulin dependence. This data was scanned into two separate databases using Teleform software and any differences were reconciled by an audiologist by referring to the original questionnaire form. In the case that a participant reported type 1 DM, the PVAMC electronic medical records and ICD diagnosis codes were reviewed for further information and clarification. In the event that a participant's reported type of DM conflicted with notes from their physician, the physician's ICD diagnosis code was used as the final label.

Participants with ICD diagnosis codes confirming type 1 DM were removed from the study population as noted above.

The remaining participants were divided into groups based on DM status (Yes, No) and HbA1c measures, as well as insulin dependence. The non-diabetic control group was divided into two groups based on HbAlc. Non-diabetic controls were participants never diagnosed with DM with HbAlc measurements ≤ 5.6% while participants never diagnosed with DM with an HbA1c between 5.7 – 6.4% were labeled as prediabetics, in accordance with ADA prediabetic levels. Members of the diabetic group were individuals diagnosed with DM by a physician. The diabetic group was not limited to individuals with an HbA1c measurement ≥ 6.5%, which represents the ADA criteria for DM, because it would have eliminated well-controlled diabetics thereby skewing the results. Furthermore, all diabetic participants, regardless of HbA1c level, were broken down into two groups based on self-reported insulin dependence and labeled as insulin dependent (IDDM) or non-insulin dependent (NIDDM).

Pure-tone thresholds were converted into 4 continuous variables for analysis: best-ear 250 Hz, best-ear standard pure-tone average (PTA), best-ear high frequency PTA, and best-ear ultra high frequency PTA. The best-ear 250 Hz measure was calculated by taking the lower threshold between the ears for each participant. The best-ear standard PTA was calculated by taking the average of the lowest thresholds between the ears for each participant at 500, 1000, and 2000 Hz. Similarly, the best-ear high frequency PTA and best-ear ultra high frequency PTA were calculated by taking the average of the lowest thresholds between the ears for each participant at 3000, 4000, 6000 and 8000 Hz and at 10000, 12500, and 14000 Hz.

Data Analysis

In regards to both of the specific aims, the diagnosis of DM (non-diabetics, prediabetes, and DM) and insulin dependence (non-diabetics, NIDDM, and IDDM) are the primary, categorical independent variables. All continuous variables will be assessed for a normal distribution utilizing the Shapiro-Wilk test and histograms. Furthermore, the relationship between age and DM status and potential confounders such as age and BDI scores will be assessed using analysis of variance (ANOVA). While all attempts were made to exclude individuals with neurological conditions, a small number of participants subjectively reported head injury or stroke. They met all other criteria, including the minimum score on the cognitive screener, so their data was included. These potential confounds for cognitive measures, the presence of stroke and traumatic brain injury (TBI), were examined as categorical variables using chi-square test to ensure there were no significant differences between groups and it was appropriate to include them in the larger group analysis.

Specific aim 1. *Determine whether Veterans with type 2 DM demonstrate greater deficits in the ability to process auditory stimuli at cognitive levels as compared to Veterans without DM.* The main outcome variables were the DSS, LNS, and P300. The main explanatory variables were the DM diagnosis and insulin dependence. Descriptive statistics were calculated by diabetic group. An ANOVA was used to compare the mean scores of each outcome variable by each explanatory variable. If the outcome variables significantly deviated from a normal distribution or had unequal variances across the group, the non-parametric correlate to a one-way ANOVA (Kruskal-Wallis) was used. If the main effect was significant (F-statistic), then a post-hoc analysis using a Bonferroni adjustment was used to determine which means were significantly different across diabetic group. Comparisons across groups were adjusted for age

and hearing using generalized linear models (GLMs). Note that because there was no relationship between BDI scores and DM status, the potential confounder BDI was left out of the models. Both crude and adjusted p-values of the main effects were reported. Model fits were assessed using studentized residuals. Significance was defined at the .05 level.

Specific aim 2. *Determine whether Veterans with type 2 DM demonstrate impaired hearing measured using pure-tone thresholds and speech understanding performance scores as compared to Veterans without DM.* To explore this aim, the main outcome variables are the 4 pure-tone variables described above, the QuickSIN, and 2 time-compressed speech measures. Similar to aim 1, the main exploratory variables were diabetic diagnosis and insulin dependence. Descriptive statistics were calculated by group. An ANOVA was used to compare the mean scores of each outcome variable by each explanatory variable. If the outcome variables significantly deviated from a normal distribution or had unequal variances across group, the non-parametric Kruskal-Wallis was used. If the main effect was significant (F-statistic), then a post-hoc analysis using a Bonferroni adjustment was used to determine which means were significantly different across groups. For the pure-tone variables, comparisons across groups were adjusted for age using GLMs. For the speech measures, GLMs were adjusted for age, hearing, and cognitive levels. Both crude and adjusted p-values of the main effects were reported. Model fits were assessed using studentized residuals. Significance was defined at the .05 level.

CHAPTER 4: RESULTS

Participant Characteristics

Of the 144 subjects enrolled, 13 had late onset type 1 DM of non-genetic origin and were excluded from this analysis to focus solely on type 2 DM effects on hearing and cognition. Lastly, one subject was missing their HbA1c value and was removed from the analysis. This left 130 subjects for analysis. After organizing participants into the two groups discussed above, there were 130 participants (n = 130) in the group based on the ADA HbA1c levels (50 non-diabetics, 23 prediabetics, and 57 diabetics) and 107 participants (n = 107) in the insulin dependence group (50 non-diabetic controls, 26 NIDDM, and 31 IDDM).

Participant characteristics are displayed in Table 1. Recruited participants ages ranged from 25 to 73 years old. Age was unsimilarly distributed across groups in both the ADA category (p = 0.006) and the insulin dependence category (p = 0.011). Post hoc analysis using a Bonferroni correction to control for familywise error rate indicated a significant, $p < .01$, difference between the non-diabetics and the prediabetics in the ADA categories and between the non-diabetics and the IDDM group in the insulin dependence category. Removal of outliers to normalize age distribution did not significantly affect the outcome measures and, thus, all participants were left in the final analyses. However, varying age distributions among groups suggests age-adjustment is necessary to control for age effects associated with outcomes.

Participants were overwhelmingly male due to the nature of the military Veteran population. Nonetheless, gender was similarly distributed across groups in both categories. Incidence of depression based on BDI scores was insignificant ($p > .05$) across groups within each category. All participants scored at or above 24 to pass the MMSE in order to rule out major cognitive deficits. In addition, HbA1c and duration of disease were both significantly ($p <$

.05) different within groups in the two categories; however, this was expected and logical based on the experiment's design. The ADA group was organized by HbA1c, and IDDM is associated with a longer duration of DM and higher HbA1c levels. Lastly, the presence of stroke did not significantly ($p > .05$) impact distribution among groups as indicated by chi-square test. However, the presence of TBI did significantly ($p > .05$) impact distribution in the insulin dependence group as indicated by chi-square test. Participants with TBI history were removed from the analysis and all outcome measures were reevaluated, it was determined that these individuals did not significantly impact the outcome of the final results and therefore were included in the final analysis. TBI reporting was added after the first 15 participants were interviewed; as such, TBI data was labeled as missing for 5 non-diabetic controls, 5 diabetics, 2 NIDDM, and 3 IDDM participants.

For the remainder of this section, results will be discussed in terms of aim and further dissected in terms of categorization. As noted above, a series of univariate one-way ANOVAs was initially performed to explore the data as well as provide context for comparison to studies in the literature that did not use statistical methods that adjusted for confounding covariates. Only the p-values from the univariate analysis will be displayed in this results section. The univariate statistics, including F-statistic (or non-parametric equivalent), degrees of freedom (between-groups), degrees of freedom (within-groups), p-values, and omega squared (ω^2) effect size can be fully viewed in appendix A. The omega squared (ω^2) effect size statistic was chosen because it is based on the mean-squared error in addition to the sum of squares, while the R^2 effect size statistic is solely based on the sum of squares (Field, 2009). This preliminary analysis was followed by multivariate investigation to control for confounding variables which will be reported in the section below and throughout the rest of this document.

Table 1

Participant Characteristics

	ADA Categories				Insulin Dependence			
	Non-Diabetic	*PreDiabetic*	*Diabetic*	*P-Value*	*Non-Diabetic*	*NIDDM*	*IDDM*	*P-Value*
Number	50	23	57		50	26	31	
Age								
Mean	44.42	52.74	49.02	0.006*	44.42	46.04	51.52	0.011*
(SD)	(11.72)	(11.61)	(9.04)		(11.71)	(7.60)	(9.50)	
Range	24-64	27-73	30-70		24-64	36-70	30-67	
Gender								
Male	47 (94.00%)	20 (86.96%)	53 (92.99%)	0.558[1]	47 (94.00%)	24 (92.31%)	29 (93.55%)	0.960[1]
Female	3 (6.00%)	3 (13.04%)	4 (7.01%)		3 (6.00%)	2 (7.69%)	2 (6.45%)	
HbA1c								
Mean	5.34	5.93	7.74	0.000[0]	5.34	6.81	8.53	0.000[0]
(SD)	(.21)	(.21)	(1.78)		(.21)	(1.01)	(1.91)	
Range	4.80-5.60	5.70-6.60	5.60-13.80		4.80-5.60	5.60-9.60	5.80-13.80	
BDI								
Mean	10.48	10.48 (8.97)	10.35	0.997*	10.48	11.42	9.45	0.691*
(SD)	(9.66)		(7.64)		(9.66)	(7.68)	(7.60)	
Range	0-36	0-35	0-32		0-36	0-27	0-32	
Duration								
Mean	N/A	N/A	8.33	.000	N/A	5.19	10.96	0.000[0]
(SD)			(6.86)			(4.97)	(7.18)	
TBI								
Yes	0	0	3 (5.26%)	0.139[1]	0	0	3 (9.68%)	0.025[1]
No	45 (100%)	23 (100%)	50 (94.74%)		45 (100%)	24 (100%)	26 (90.32%)	
Stroke								
Yes	0	1 (4.34%)	2 (3.5%)	0.373[1]	0	0	2 (6.45%)	0.082[1]
No	50 (100%)	22 (95.66%)	55 (96.5%)		50 (100%)	26 (100%)	29 (93.55%)	

Note. BDI = Beck Depression Inventory; TBI = Traumatic Brain Injury; Age and Duration are measured in years; * = One-way ANOVA; [0] = Kruskal-Wallis; [1] = Chi Square

Specific Aim 1 Results

ADA category results. This section will focus on the Aim 1 outcome measures, behavioral cognitive measures and electrophysiologic measures, by the ADA categories.

***Cognitive behavioral measures*.** Table 2 indicates the mean and range of DSS and LNS scores for participants organized by the ADA categories as well as the p-value from the one-way ANOVA and the age-adjusted p-value from the GLMs. As displayed visually in Figures 1 and 2, diabetics and prediabetics had poorer scores than non-diabetics on both the DSS and LNS.

Initial GLMs revealed that the potential cofounding variable, age, was significantly ($p < .001$) associated with DSS and LNS scores while the potential confounding variable, hearing loss, was not significantly ($p > .05$) related to DSS and LNS scores; therefore, the covariate, hearing loss, was removed from the final GLMs. The final GLMs revealed the covariate, age, was significantly related to DSS scores (Wald χ^2 (1) = 28.110, $p = .000$), and LNS scores (Wald χ^2 (1) = 19.465, $p = .000$). However, after adjusting for age, there was no significant main effect of DM on DSS scores (Wald χ^2 (2) = 2.962, $p = .227$) nor LNS scores (Wald χ^2 (2) = 1.087, $p = .581$). Age-adjusted comparisons between subjects with pre-diabetes to controls and subjects with diabetes to controls are shown in Table 3. Here, the effect sizes are consistent with the model parameter estimates and the p-values are shown for the individual contrasts. Although of borderline statistical significance ($p = .09$), it appears that Veterans with diabetes perform worse on the DSS than controls after adjusting for age. The diabetes-related decline in the digit-symbol performance was on average about 5.

Table 2

DSS and LNS Scores by ADA Categories

	ADA Categories			*P-Value*	*Age-Adjusted P-Value*
	Non-Diabetic	*Prediabetic*	*Diabetic*		
DSS					
Mean	69.00	61.78	61.16 (16.23)	0.035	0.227
(SD)	(16.10)	(16.27)			
Range	40-113	32-109	32-99		
LNS					
Mean	12.00	10.70	10.95 (2.89)	0.122	0.581
(SD)	(2.66)	(4.12)			
Range	6-18	3-17	5-20		

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing

Table 3

Effect Sizes for DSS and LNS Scores by ADA Categories

	DSS Score			**LNS Score**		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	97.599	5.77	0.000	16.624	1.12	0.000
Non-Diabetics	0.000	N/A	N/A	0.000	N/A	N/A
Prediabetics	-1.861	3.80	0.624	-0.438	0.74	0.552
Diabetics	-4.865	2.87	0.090	-0.574	0.56	0.303
Age	-0.644	0.12	0.000	-0.104	0.024	0.000

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

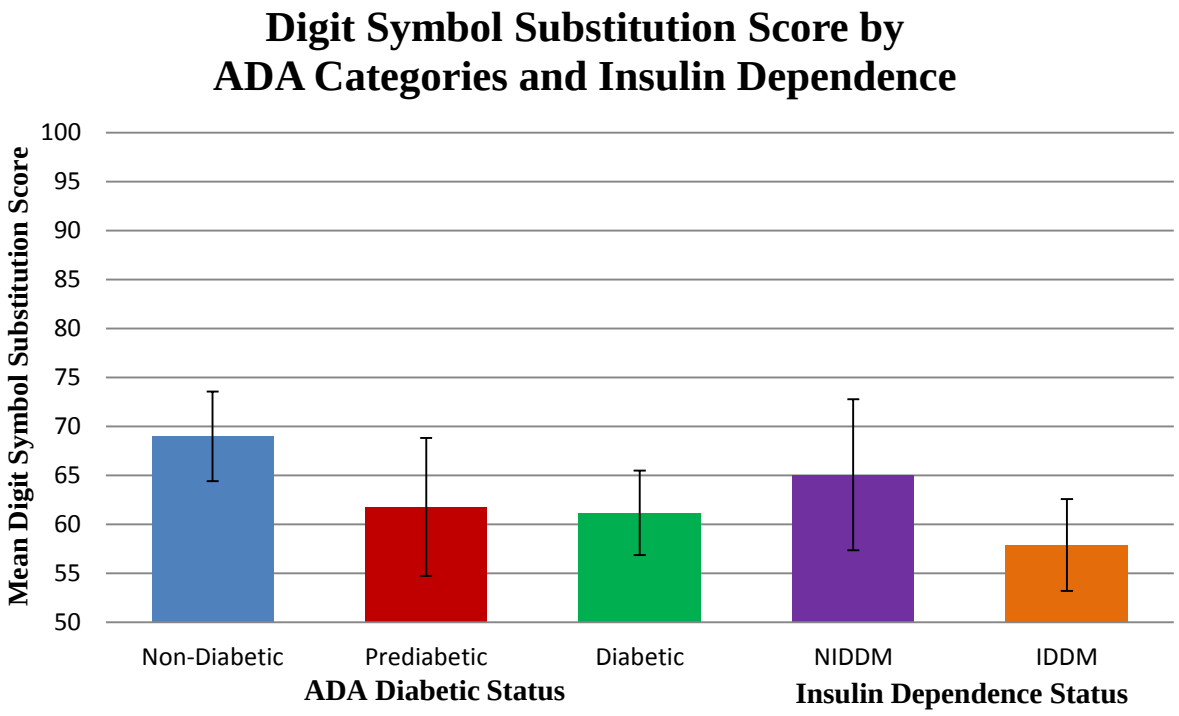

Figure 1. Mean raw DSS scores by ADA categories and insulin dependence. Error bars represent 95% confidence interval. After controlling for age, there were no significant differences in either categorization method; however, individuals with prediabetes and diabetes had poorer scores, on average, than controls. Further, among diabetics, the IDDM group had the poorest scores.

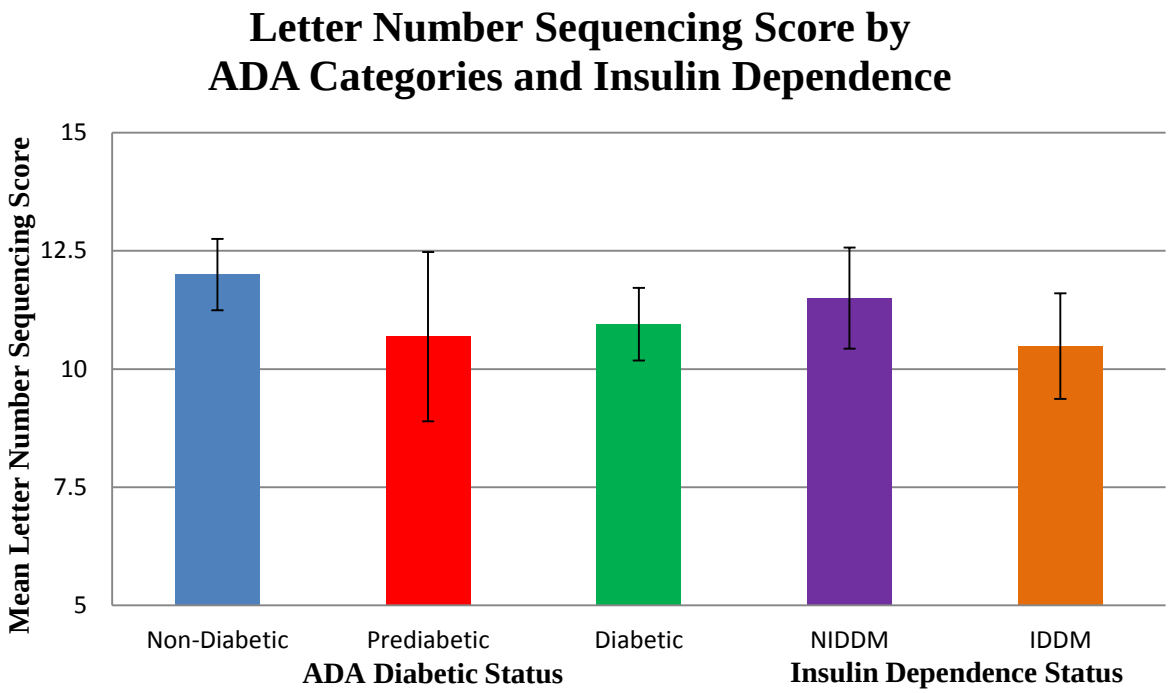

Figure 2. Mean raw LNS scores by ADA categories and insulin dependence. Error bars represent 95% confidence interval. After controlling for age, there were no significant differences in either categorization method; however, individuals with prediabetes and diabetes had poorer scores, on average, than controls. Further, among diabetics, the IDDM group had the poorest scores.

Electrophysiologic measures. P300 measures were taken on 101 participants in the ADA categories: 39 non-diabetics, 20 prediabetics, and 42 diabetics. The number of participants included for P300 analysis is smaller as participants who could not remain awake and alert during the measure were removed; this will also be reflected in the number analyzed for the insulin dependence categorization method. Table 4 displays the mean latency and amplitude values for participants organized by the ADA categories as well as the p-value from the one-way ANOVA and the age and hearing adjusted p-value from the GLMs. Age has a well-documented relationship with P300 measures and, despite being a suprathreshold measure, even relatively

slight hearing differences have been demonstrated to affect P300 measures (Cooray et al., 2008; Cosway et al., 2001; Kurita et al., 1995; Kyizom et al.,2010; Oates, Kurtzberg, & Stapells, 2002; Pozzessere et al.,1991). Oates, Kurtzberg, and Stapells (2002) reported significantly different P300 latencies between groups of normal hearing subjects and age-matched peers with slightly poorer mild hearing losses. Age was significantly related to latency of the P300 (Wald χ^2 (1) = 13.786, p = .000) and standard PTA was not (Wald χ^2 (1) = .495, p = .482). After controlling for age and hearing, there was no significant main effect of DM on P300 latency (Wald χ^2 (2) = 1.623, p = .444). However, the covariate age was significantly related to the amplitude of the P300 (Wald χ^2 (1) = 4.072, p = .044) as was the covariate standard PTA significantly related to amplitude measurement (Wald χ^2 (1) = 5.767, p = .016). The relationship between age and P300 amplitude, and hearing and P300 amplitude can be seen in Figure 3. Most notably, after controlling for age and hearing, there was a significant main effect of DM on the amplitude of the P300 (Wald χ^2 (2) = 6.092, p = .048). Inspection of individual contrasts suggest this difference is between controls and Veterans with pre-diabetes (p = .043); specifically Veterans with pre-diabetes yield P300 amplitudes that were 1.936 (metric) greater than controls after adjusting for age and hearing. The effect sizes, standard error of the effect size, and associated p-values for all contrasts are reported in Table 5.

Table 4

P300 Latency and Amplitude by ADA Categories

	ADA Categories				
	Non-Diabetic	*Prediabetic*	*Diabetic*	*P-Value*	*Age- and Hearing-Adjusted P-Value*
Latency					
Mean (SD)	347.49 (53.21)	375.00 (47.32)	360.43 (45.95)	0.123	0.444
Amplitude					
Mean (SD)	5.13 (3.43)	6.47 (4.37)	4.34 (3.45)	0.103	0.048

Note. Latency is measured in msec; Duration is measured in µV

Table 5

Effect Sizes for P300 Measures by ADA Categories

	P300 Latency			**P300 Amplitude**		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	263.275	22.10	0.000	9.906	1.66	0.000
Non-Diabetics	0.000	N/A	N/A	0.000	N/A	N/A
Prediabetics	15.486	12.72	0.224	1.936	0.96	0.043
Diabetics	8.650	10.16	0.395	-0.335	0.76	0.662
Age	1.682	0.45	0.000	-0.069	0.03	0.044
Hearing	0.58	0.83	0.482	-0.150	0.06	0.016

Note. Latency is measured in msec; Duration is measured in µV; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

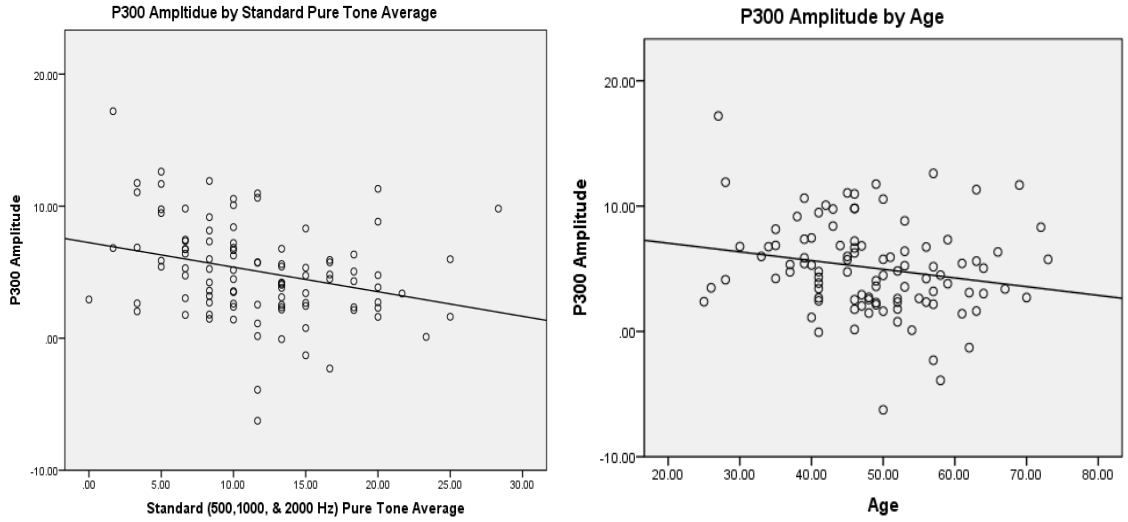

Figure 3. Raw data relating P300 amplitude to age and hearing. Across all participants increased age was associated with decreased P300 amplitude.

Insulin dependence results. This section will focus on the Aim 1 outcome measures by the insulin dependence categorization method.

Cognitive behavioral measures. Table 6 displays the mean, range and p-values of the DSS and LNS scores for participants organized by insulin dependence. As seen above, in Figures 1 and 2, NIDDMs and IDDMs had poorer scores than non-diabetics with IDDMs having the poorest overall scores among any group for both the DSS and LNS. Similar to the ADA categories, initial GLMs revealed that the potential cofounding variable, age ,was significantly ($p < .001$) associated with DSS and LNS scores while the potential confounding variable, hearing loss, was not significantly ($p > .05$) related to DSS and LNS scores and was therefore removed from the final GLMs. Final GLMs, revealed that the covariate, age, was significantly related to DSS scores (Wald χ^2 (1) = 24.225, $p = .000$) and LNS scores, (Wald χ^2 (1) = 17.534, $p = .000$). Moreover, there were no significant main effects of insulin dependence on DSS scores (Wald χ^2 (2) = 3.470, $p = .176$) nor on the LNS scores (Wald χ^2 (2) = 1.730, $p = .421$). Table 7 lists the

effect sizes, standard error of the effect size, and associated p-values for all contrasts. Notably, the IDDM group was marginally statistically significantly (p =.06) different from the controls on the age-adjusted DSS score. The decline in DSS score associated with IDDM was approximately 6.

Figure 4 visualizes the relationship between the cognitive behavioral scores and age for the entire participant population as the covariate age significantly affected the DSS and LNS scores regardless of categorization method. In Figure 4, there is a negative correlation between age and DSS scores whereby the scores are poorer as age increases. Similarly there is a negative correlation between age and the LNS scores.

Table 6

DSS and LNS Scores by Insulin Dependence

	Insulin Dependence Status				
	Non-Diabetic	*NIDDM*	*IDDM*	*P-Value*	*Adjusted P-Value*
DSS					
Mean (SD)	69.00 (16.10)	65.08 (19.12)	57.90 (12.76)	0.012	0.176
Range	40-113	32-99	34-85		
LNS					
Mean (SD)	12.00 (2.66)	11.50 (2.64)	10.48 (3.05)	0.061	0.421
Range	6-18	8-18	5-20		

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing

Table 7

Effect Sizes for DSS and LNS Scores by Insulin Dependence

	DSS Score			LNS Score		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	98.910	6.40	0.000	16.520	1.14	0.000
Non-Diabetics	0.000	N/A	N/A	0.000	N/A	N/A
NIDDM	-2.833	3.46	0.413	-0.335	0.614	0.585
IDDM	-6.319	3.40	0.063	-0.794	0.60	0.189
Age	-0.673	0.14	0.000	-0.102	0.02	0.000

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

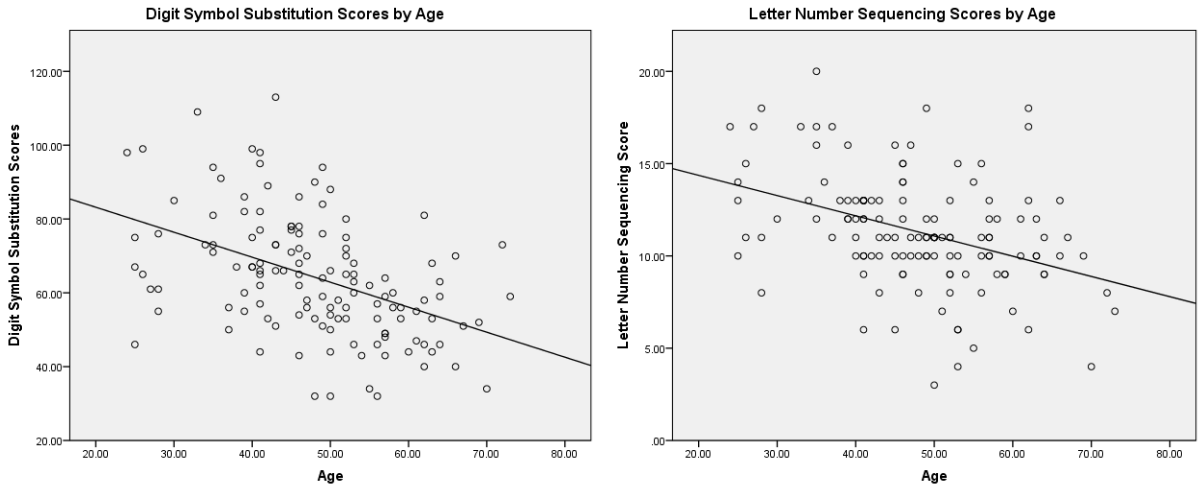

Figure 4. Raw data relating DSS and LNS scores to age. As expected, there was a significant association between DSS and LNS scores and age whereas increased age was associated with poorer scores.

Electrophysiologic measures. P300 measures were taken on 81 participants in the insulin dependence categories (39 non-diabetics, 20 NIDDM, and 22 IDDM). Once again, the number of

participants included for analysis is smaller due to the removal of participants who could not remain awake and alert for the length of the task. Table 8 displays the mean latency and amplitude values for participants organized by insulin dependence as well as the p-value from the one-way ANOVA and the age and hearing adjusted p-value from the GLMs. The covariate age was significantly related to latency of the P300 (Wald χ^2 (1) = 9.230, p = .002) while standard PTA was not (Wald χ^2 (1) = .796, p = .372). There was no significant main effect of insulin dependence on latency measures (Wald χ^2 (2) = .637, p = .727). In addition, the covariate age was not significantly related to the amplitude of the P300 (Wald χ^2 (1) = 3.235, p = .072) nor was the covariate standard PTA (Wald χ^2 (1) = 2.398, p = .121). Lastly, there was no significant main effect of DM on the amplitude of the P300 (Wald χ^2 (2) = .343, p = .843). Table 9 displays effect sizes and parameter estimates based on GLM.

Table 8

P300 Latency and Amplitude by Insulin Dependence

	Insulin Dependence Status				
	Non-Diabetic	*NIDDM*	*IDDM*	*P-Value*	*Adjusted P-Value*
Latency					
Mean (SD)	347.49 (53.21)	357.55 (45.24)	363.05 (47.49)	0.478	0.727
Amplitude					
Mean (SD)	5.13 (3.43)	4.64 (2.77)	4.07 (4.02)	0.516	0.843

Note. Latency is measured in msec; Duration is measured in µV

Table 9

Effect Sizes for P300 Measures by Insulin Dependence

	P300 Latency			P300 Amplitude		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	260.829	25.95	0.000	9.533	1.85	0.000
Non-Diabetics	0.000	N/A	N/A	0.000	N/A	N/A
NIDDM	9.315	12.62	0.460	-0.361	0.90	0.687
IDDM	6.864	12.54	0.584	-0.482	0.89	0.589
Age	1.669	0.55	0.002	-0.070	0.04	0.072
Hearing	0.87	0.98	0.372	-0.108	0.07	0.121

Note. Latency is measured in msec; Duration is measured in μV; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

Specific Aim 2 Results

ADA category results. Similar to the results for Aim 1, Aim 2 results will be discussed in terms of categorization method. This section will focus on the Aim 2 outcome measures, audiometric data and speech recognition tests, by the ADA categories. Notably, all participants in both categories had normal tympanometry and no air bone gaps indicating the absence of a conductive component among audiometric results.

Audiometric data. Table 10 represents the mean, range, and p-values of the 4 PTA group thresholds based on organization by the ADA categories. Diabetics had poorer mean thresholds at 250Hz (12.19 dB HL) and at the standard PTA (13.10 dB HL) compared to non-diabetics and prediabetics, while prediabetics had the poorest mean thresholds at the high frequency PTA (24.02 dB HL) and ultra-high frequency PTA (55.83 dB HL). Note that one prediabetic participant did not complete ultra-high frequency testing and their data point was excluded during statistical analysis.

The covariate, age, was significantly associated with the 250 Hz measurement (Wald χ^2 (1) = 6.248, p = .012) and there was a borderline significant main effect of DM on the 250 Hz measurement (Wald χ^2 (2) = 5.449, p = .066). Parameter estimates revealed a significant, p = .021, difference between the control and the diabetic group. After adjusting for age, Veterans with DM had 2.6 dB poorer thresholds at 250 Hz compared to controls. For the standard PTA measure, age was significantly associated with standard PTA (Wald χ^2 (1) = 14.646, p = .000) while there was a marginally significant main effect of DM on standard PTA (Wald χ^2 (2) = 4.566, p = .102). As seen in Table 11, model parameter estimates revealed a significant (p = .05) difference between Veterans with DM and the control group whereby after adjusting for age, the DM group had standard PTA thresholds approximately 2 dB poorer compared to controls. Lastly, for the high frequency PTA and the ultra high frequency PTA, the covariate, age, was significantly related to the audiometric measure (p = .000) while the main effect of DM was insignificantly (p > .05) related to the measure.

Table 10

Auditory Pure-Tone Measures by ADA Categories

	ADA Categories				
	Non-Diabetic	*Prediabetic*	*Diabetic*	*P-Value*	*Adjusted P-Value*
250 Hz					
Mean	9.00	11.09	12.19	0.024	0.066
(SD)	(4.95)	(7.06)	(6.34)		
Range	0.00-25.00	0.00-30.00	0.00-25.00		
Standard PTA					
Mean	10.07	11.59	13.10	0.043	0.102
(SD)	(4.97)	(6.25)	(7.00)		
Range	1.67-25.00	3.33-33.33	-3.33-33.33		
High PTA					
Mean	16.68	24.02	18.73	0.120	0.641
(SD)	(13.93)	(18.31)	(12.15)		
Range	0.00-61.25	0.00-67.50	-1.25-46.25		
Ultra High PTA					
Mean	41.43	55.83	53.22	0.044	0.506
(SD)	(26.26)	(33.78)	(8.73)		
Range	-5.00-105.00	3.33-103.33	1.67-110.00		

Note. 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; All pure-tone averages reported in dB HL

Table 11

Effect Sizes for Audiometric Data by ADA Categories

	250 Hz			***Standard PTA***			***High PTA***			***Ultra High PTA***		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	3.630	2.30	0.114	1.907	2.30	0.406	-16.835	4.55	0.000	-38.288	7.95	0.000
Non-Diabetics	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
Pre-diabetics	1.081	1.51	0.474	-0.001	1.51	1.000	1.071	2.99	0.720	-1.488	5.30	0.779
Diabetics	2.637	1.14	0.021	2.188	2.30	0.055	-1.415	2.26	0.531	3.532	3.93	0.369
Age	0.121	0.05	0.012	0.184	0.05	0.000	0.754	0.10	0.000	1.795	0.17	0.000

Note. 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; All pure-tone averages reported in dB HL; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

Speech recognition tests. Table 12 displays the speech measures for the ADA categories. All 3 speech measures (the QuickSin, 50% time compressed speech and 60% time compressed speech) were heavily skewed due to a ceiling effect and failed the Shapiro-Wilk test of normality. The non-parametric one-way ANOVA equivalent, the Kruskal-Wallis, was used for univariate analysis (p-values located in Table 12). Because speech measures were essentially normal based on the limits of the tests across groups and it is known that speech measures are affected by cognitive and hearing ability, the potential confounding covariates age, cognition (based on the DSS score), and hearing (based on the Standard PTA) were all included in GLMs to reveal effect sizes for each variable. GLMs revealed that the covariate, age, was significantly ($p < .01$) associated with each of the speech measures while the effect of DM was insignificant on the QuickSin (Wald χ^2 (2) = .564, p = .754), 50% time compressed speech (Wald χ^2 (2) = 1.262, p = .532), and on 60% time compressed speech (Wald χ^2 (2) = .822, p = .663). Additionally, the influence of cognition, based on the DSS score, and hearing, based on the standard PTA, were insignificant across all three measures ($p > .05$). Table 13 reveals effect sizes. However, based on the abnormal residuals of this model, further transformation of the data is needed.

Table 12

Speech Measures by ADA Categories

	ADA Categories				
	Non-Diabetic	*Prediabetic*	*Diabetic*	*P-Value*	*Adjusted P-Value*
QuickSIN					
Mean	.76	1.15	.94	0.426^{0}	0.754
(SD)	(1.56)	(1.67)	(1.58)		
Range	-1.5-5	-1.5-4	-2.5-7		
TCS 50%					
Mean	94.16	89.09	91.93	0.637^{0}	0.532
(SD)	(5.52)	(15.54)	(8.73)		
Range	78-100	50-100	64-100		
TCS 60%					
Mean	90.64	85.55	88.18	0.231^{0}	0.663
(SD)	(8.86)	(12.66)	(11.61)		
Range	60-100	58-100	44-100		

Note. TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; ^{0} = Kruskal-Wallis

Table 13

Effect Sizes for Speech Measures by ADA Categories

	QuickSIN			***TCS 50%***			***TCS 60%***		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	-1.491	1.02	0.143	98.708	6.14	0.000	102.226	7.06	0.000
Non-Diabetics	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
Pre-diabetics	-0.159	0.37	0.671	-2.400	2.26	0.288	-2.001	2.60	0.442
Diabetics	-0.211	0.28	0.459	-0.194	1.72	0.910	0.220	1.97	0.911
Age	0.055	0.01	0.000	-0.223	.08	0.007	-0.266	0.10	0.005
Cognition	-.007	0.01	0.439	0.092	0.05	0.078	0.054	0.06	0.370
Hearing	0.028	0.02	0.189	-0.98	0.13	0.455	-0.344	0.15	0.022

Note. 250 Hz = TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

Insulin dependence results. This section will focus on the Aim 2 results by insulin dependence.

Audiometric data. Table 14 displays the mean, range, and p-values of the 4 PTA group thresholds based on organization by the insulin dependence. GLMs revealed the covariate age was significantly associated with the 250 Hz measurement (Wald χ^2 (1) = 7.647, p = .006) and there was a significant main effect of DM on the 250 Hz measurement (Wald χ^2 (2) = 8.412, p = .015). Parameter estimates revealed the effect was significant (p = .004) between the control non-diabetic group and the IDDM group only whereby Veterans with DM had 3.7 dB poorer thresholds at 250 Hz compared with their non-diabetic peers. Moreover, the covariate age was significantly associated with standard PTA (Wald χ^2 (1) = 15.850, p = .000) and there was a main effect of DM on standard PTA (Wald χ^2 (2) = 5.850, p = .050). Again, parameter estimated revealed this effect was significant (p = .01) between the IDDM and non-diabetic group; effect size revealed IDDM standard PTA scores were 3.1 dB poorer than those of non-diabetics. Similar to the ADA categories, the covariate, age, was significantly related to the high frequency

PTA and the ultra high frequency PTA, ($p < .001$) while there was no significant ($p > .05$) main effect of insulin dependence on high-frequency PTA and ultra-high frequency PTA (see Table 14). Effect sizes are reported in Table 15.

Table 14

Auditory Pure-Tone Measures by Insulin Dependence

	Insulin Dependence Status				
	Non-Diabetic	*NIDDM*	*IDDM*	*P-Value*	*Adjusted P-Value*
250 Hz					
Mean	9.00	10.38	13.71	0.002	0.015
(SD)	(4.95)	(5.99)	(6.32)		
Range	0.00-25.00	0.00-20.00	0.00-25.00		
Standard PTA					
Mean	10.07	11.15	14.73	0.004	0.054
(SD)	(4.97)	(6.66)	(6.95)		
Range	0.00-25.00	-3.33-28.33	3.33-33.33		
High PTA					
Mean	16.68	16.30	20.77	0.314	0.848
(SD)	(13.93)	(11.85)	(12.21)		
Range	0.00-61.25	-1.25-46.25	2.50-45.00		
Ultra High PTA					
Mean	41.43	47.82	57.74	0.028	0.561
(SD)	(26.26)	(21.82)	(29.21)		
Range	-5.00-105.00	1.67-95.00	3.33-110.00		

Note. 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; All pure-tone averages reported in dB HL

Table 15

Effect Sizes for Audiometric Data by Insulin Dependence

	250 Hz			***Standard PTA***			***High PTA***			***Ultra High PTA***		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	2.688	2.41	0.264	0.677	2.30	0.785	-13.62	4.84	0.005	-31.974	8.84	0.000
Non-Diabetics	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
NIDDM	1.155	1.30	0.374	0.745	1.34	0.579	-1.481	2.61	0.571	3.713	4.78	0.437
IDDM	3.701	1.28	0.004	3.164	1.32	0.017	-0.749	2.57	0.771	4.582	4.70	0.330
Age	0.142	0.05	0.006	0.211	0.05	0.000	0.682	0.10	0.000	1.653	0.19	0.000

Note. 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; All pure-tone averages reported in dB HL; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

Speech recognition tests. Table 16 shows the speech measures for the insulin dependence categories. Once again, all 3 speech measures (the QuickSin, 50% time compressed speech and 60% time compressed speech) violated the law of normality. Kruskal-Wallis results can be seen in Appendix A. Moreover, GLMs revealed that the covariate, age, was significantly (p <.01) associated with each of the speech measures while the main effect of DM was insignificant on the QuickSin (Wald χ^2 (2) = 1.537, p = .464), 50% time compressed speech (Wald χ^2 (2) = 236, p = .889), and on 60% time compressed speech (Wald χ^2 (2) = .010, p = .995). In addition, the influence cognition, based on DSS score, on all 3 speech measures was insignificant (p > .05). However, the influence of hearing, based on standard PTA, on the QuickSIN and 50% time-compressed speech was insignificant (p > .05) but was significant for 60% time-compressed speech (Wald χ^2 (1) = 7.479, p = .006). Table 17 contains effect sizes. Similar to the ADA group, model residuals revealed abnormal and likely unreliable results which require further transformation of the data.

Table 16

Speech Measures by Insulin Dependence

	Insulin Dependence Status				
	Non-Diabetic	*NIDDM*	*IDDM*	*P-Value*	*Adjusted P-Value*
QuickSIN					
Mean (SD)	.76 (1.56)	.50 (1.23)	1.31 (1.76)	0.099[0]	0.464
Range	-1.50-5	-1.50-3	-2.50-7		
TCS 50%					
Mean (SD)	94.16 (5.52)	93.23 (8.22)	90.84 (9.12)	0.257[0]	0.889
Range	78-100	64-100	64-100		
TCS 60%					
Mean (SD)	90.64 (8.86)	89.69 (11.30)	86.90 (11.91)	0.314[0]	0.995
Range	60-100	46-100	44-100		

Note. TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; [0] = Kruskal-Wallis

Table 17

Effect Sizes for Speech Measures by Insulin Dependence

	QuickSIN			***TCS 50%***			***TCS 60%***		
	B	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*	*B*	*SE B*	*P-Value*
Constant	-1.515	1.13	0.179	99.515	5.42	0.000	107.764	7.53	0.000
Non-Diabetics	0	N/A	N/A	0	N/A	N/A	0	N/A	N/A
NIDDM	-0.394	0.34	0.244	-0.260	1.62	0.873	-.052	2.26	0.982
IDDM	-0.014	0.34	0.967	-0.802	1.65	0.627	0.192	2.30	0.933
Age	0.050	0.02	0.001	-0.212	0.07	0.004	-0.273	0.10	0.008
Cognition	-0.004	0.01	0.669	0.067	0.05	0.140	-0.008	0.06	0.904
Hearing	0.035	0.02	0.150	-0.058	0.12	0.621	-0.446	0.16	0.006

Note. 250 Hz = TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; *B* = regression coefficient (effect size); *SE B* = standard error of regression coefficient

CHAPTER 5: DISCUSSION

Aim 1 Discussion

The following sections will discuss the results of the behavior cognitive tests and electrophysiologic P300 measure in more detail. Outcomes from both categorization methods will be discussed simultaneously.

Cognitive behavioral measures.

Digit symbol substitution test. After adjusting for the covariate age, no significant effects of DM or insulin dependence on the DSS WAIS-III subtest were found. The results of this outcome measure were driven by the covariate, age, which had a significant impact on the DSS score in both categorization methods. Conversely, the covariate, DM, had no significant effect on the DSS score in either categorization method.

Nonetheless, on average, diabetics performed more poorly compared with their non-diabetic counterparts. Moreover, it was revealed that the IDDM and DM groups had marginally statistically significant poorer scores on the DSS compared to the non-diabetic group. In fact, the IDDM group demonstrated the poorest score, on average, of any group. Though these results were not statistically significant at these baseline measures, they were trending in the direction of statistical significance. It has been suggested that cognitive processes will decline at a faster rate among diabetics compared to non-diabetics due to the synergistic effect of aging and DM, which may suggest that DM will be a statistically significant factor in DSS scores in follow-up measurements of participants in the study (Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001). Figure 5 visually demonstrates the synergistic effect of age and DM on the DSS scores among the ADA categories and insulin dependence groups; despite age being the main influence on the DSS scores, it is still clear DM is contributing to the decline in scores as the ADA-defined

diabetics, NIDDM, and IDDM groups have noticeably sharper slopes than the non-diabetic controls.

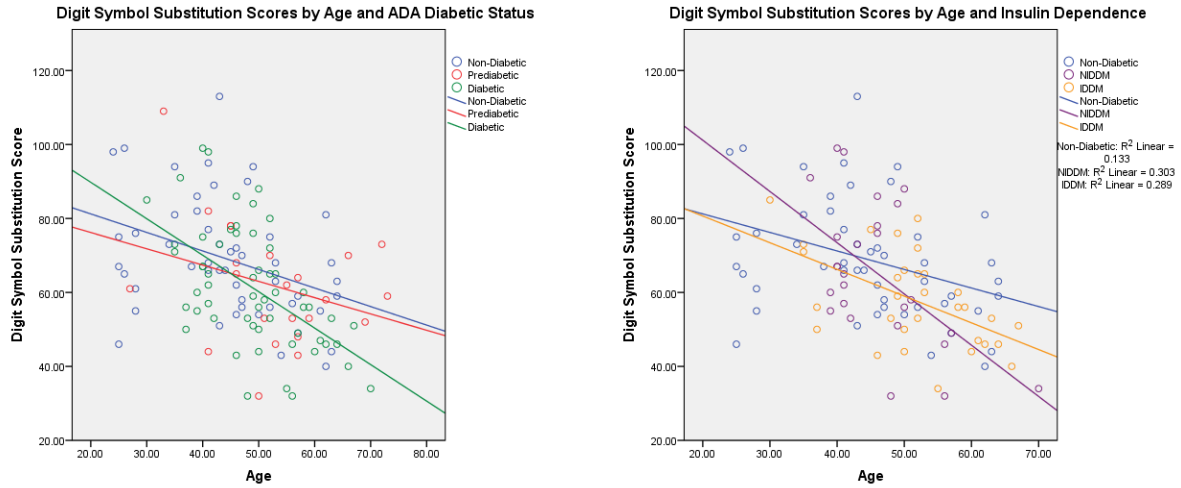

Figure 5. Raw data relating DSS score to age by ADA diabetic status and insulin dependence. Although there were no significant differences among the three groups, participants with diabetes had poorer scores on average compared with non-diabetics.

Notably, several other research groups have demonstrated statistically significant poorer DSS scores among diabetics versus their non-diabetic counterparts and have even reported a tendency toward poorer scores among those at risk for DM (Cukierman et al., 2005; Gregg et al., 2000; Vanhanen et al., 1997). However, the participants in these studies were much older than those in the present study, particularly the Vanhanen et al. (1997) and Gregg et al. (2000) studies where the participants mean ages were 67.1 ± 5.0 years and 71.8 ± 5.0 years, respectively. In fact, studies with mean ages similar to the current study have also found no significant differences regarding cognitive function between diabetics and non-diabetics. In a study of relatively younger adults (mean age = 59 year), Lowe, Trael, Wallace, & Welty (1994) failed to find evidence of cognitive deficits in adults with Type 2 DM. Similarly, Ryan and Geckle

(2000a) studied a group of younger adults (mean age = 51 years) and found no significant differences in memory and cognitive function after adjusting for the covariate age.

Letter number sequencing. There was no significant effect of DM on the LNS scores in either categorization group prior to and after adjusting for age. Similar to the DSS scores, age was revealed as the significant influential force behind declining LNS scores among subjects while the main outcome effect of DM was not significantly related to LNS scores. Little research using the LNS WASI-III subtest has been previously conducted among diabetics; however, those that have reported it found significant differences between diabetics and non-diabetics (Lin et al., 2010). However, some researchers have noted that diabetics tend to do more poorly on cognitive tests in the sub-domain of verbal memory and others have speculated it would be an area of more severe deficit, especially given the higher rate of dementia among diabetics (Cukierman et al., 2005; Kodl & Seaquist, 2008; Ryan & Geckle, 2000b). In the current study, a non-verbal, the DSS, had a more powerful statistical difference than the verbal LNS in both the ADA and insulin dependence categories.

Age effect and brain capacity. Although not statistically significantly impacted by DM after controlling for age, diabetics performed poorer than non-diabetics overall and the IDDM group represented the poorest scores of any group. The GLMs revealed effect sizes that were small; however, when these effect sizes were used to predict DSS and LNS scores given age and insulin dependence they represented an approximate 10 year age difference between non-diabetic and IDDM individuals. For example, a 45-year old non-diabetic participant would have the same DSS score as a 35-year old IDDM participant. This concept is visualized Figures 6 and 7. This phenomenon is in agreement with statements made by several researchers who theorized DM is effectively impacting individuals by increasing the rate of cognitive decline, which may appear

to be a more rapid cognitive aging process (Kodl & Seaquist, 2008; Ryan & Geckle, 2000a; Ryan & Geckle, 2000b).

In a review of literature, Ryan and Geckle (2000b) theorized that relatively younger adults (e.g. < 65 years of age) were protected from the impact of DM on cognitive impairment by their greater brain reserve capacity as neuro-imaging research has demonstrated the rate of cortical atrophy nearly doubles between the ages of 65 and 75 years in otherwise healthy subjects and beginning at age 60, structures vital to memory and learning such as the hippocampus and amygdala show a significant decrease in volume in healthy adults (Mu, Xie, Wen, Weng, & Shuyun, 1999; Pirttilä, Järvenpää, Laippala, & Frey, 1992; Ryan & Geckle, 2000b). It is possible that the impact of DM in older adults (e.g. > 65 years of age), with little brain reserve, is one where it accelerates the aging effects on cognitive function while younger adults remain relatively less affected. This may serve as a theory as to why the cognitive behavioral measures of participants in this study, where the mean age was much younger than 60-65 years, were not significantly impacted by DM.

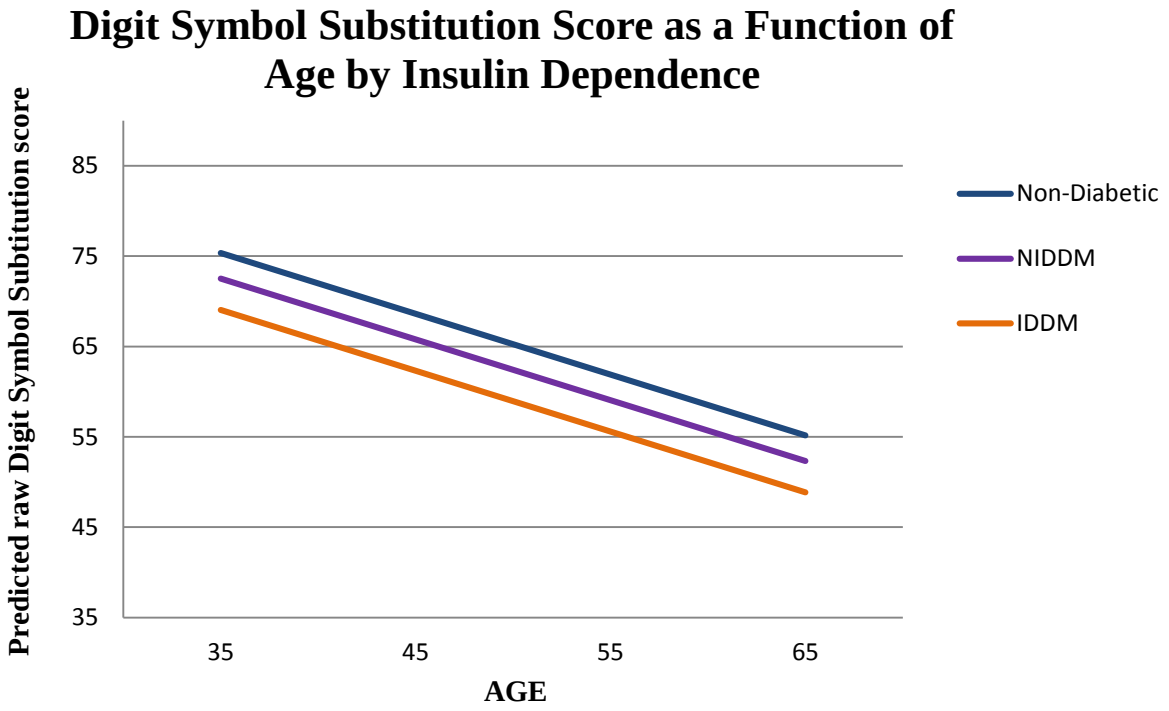

Figure 6. Predicted DSS score given age and insulin dependence. Using effect sizes from the GLM model, DSS scores are predicted by age and insulin dependence status. The IDDM group has the poorest scores and represents the score of a non-diabetic individual approximately 10 years older.

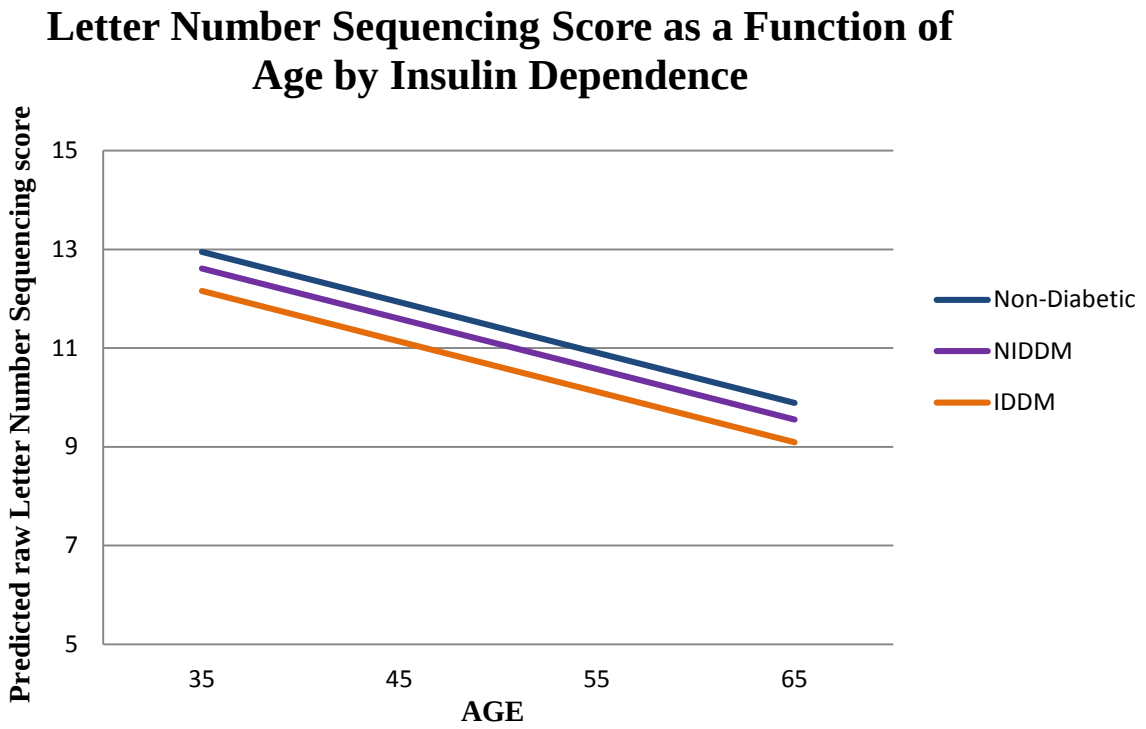

Figure 7. Predicted LNS score given age and insulin dependence. Using effect sizes from the GLM model, LNS scores are predicted by age and insulin dependence status. The IDDM group has the poorest scores and similar to the DSS scores, represent an approximate 10 year age difference between groups.

Electrophysiologic measures. The auditory-evoked P300 electrophysiologic measure is the result of electrochemical changes in the neurons in response to consciously recognizing and discriminating auditory stimuli (Kurita et al. 1995; Oates et al., 2002; Pozzessere et al., 1991). It has been strongly correlated with attention and short-term memory in adults and may provide objective evidence of a participant's auditory working memory (Cooray et al., 2008; Tandon et al., 1998). The P300 can be measured in terms of latency and amplitude.

P300 latency. P300 latency is thought to reflect the speed and efficacy of processing and recognizing new stimuli in the oddball paradigm (Cooray et al., 2008; Oates et al., 2002; Tandon et al., 1998). In the present study, there was no main effect of DM on P300 latency nor was the covariate hearing related to P300 latency; however, P300 latency was significantly ($p < .05$)

related to the covariate age in both categorization methods. Although not statistically significant, diabetic participants (ADA diabetics, NIDDM, and IDDM) had longer mean latencies compared to the non-diabetic control group. The prediabetic group had the longest mean P300 latency; though, this is likely explained by this subgroup being the oldest among all groups in either categorization method. However, among the diabetic groups (ADA diabetics, NIDDM, and IDDM) the IDDM group had the longest latencies.

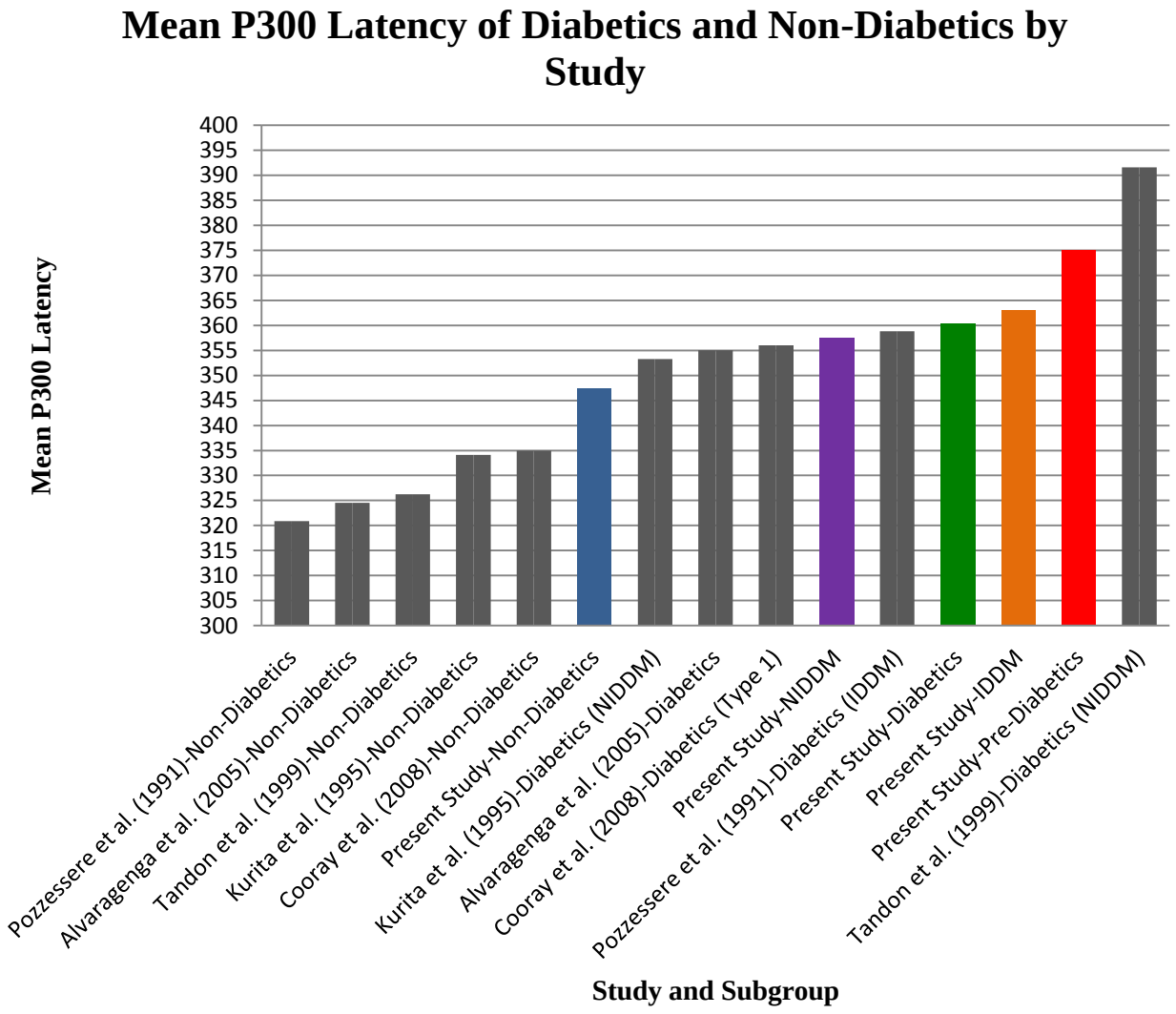

Figure 8. P300 latencies of various studies. Across several studies, diabetics have longer P300 latencies on average compared with non-diabetics.

Many other authors have reported significant differences between diabetics and non-diabetics using the latency measures of the P300 electrophysiologic measure (Alvarenga et al., 2005, Cooray et al., 2008; Kurita et al., 1995; Pozzessere et al., 1991; Tandon et al., 1999; Vanhanen et al., 1996). Figure 8 compares the mean latency of the groups in the present study to measures from several other studies. However, it should be noted that mean ages vary across groups and this figure is not meant to specifically compare measurements across studies but rather recognize general trends in studies.

It is immediately apparent that across all studies, non-diabetics have shorter P300 latencies than diabetics regardless of ages and electrode measurement. Researchers have explained this phenomenon by suggesting the long-term effect of DM is one that manifests itself as an accelerated cognitive aging process, thereby decreasing psychomotor speed and short-term memory abilities which result in a longer P300 latency (Cooray et al., 2008). Age has been repeatedly associated with decreased cognitive ability and increased P300 latency; as it was in the present study.

It is also evident that groups in the present study generally have longer latencies than those of other studies, particularly the non-diabetic group from the present study versus non-diabetics from other studies. This is likely due to the measurements for latency taken at electrode Pz in the present study while other studies used uniformly Cz (Alvarenga et al., 2005, Cooray et al., 2008; Kurita et al., 1995; Pozzessere et al., 1991; Tandon et al., 1999; Vanhanen et al., 1996). The P300 potential is mostly a frontal cortex phenomenon, thus measurements from Pz would be slightly more latent than those from Cz based on their placement on the head and the anatomy of the brain.

Without including the prediabetic group, the 2 most latent groups in Figure 8 are those from the Tandon et al. (1999) study and the IDDM group from the present study. Across studies, these two groups have the highest HbA1c levels at 9.9% ± 1.0% and 8.53% ± 1.91%, respectively. Moreover, the Tandon et al. (1999) study used a relatively young group of adults (mean age = 43.67 ± 9.00) which were even younger than the IDDM group from the present study (mean age = 51.52 ± 9.50 years). This led Tandon et al. (1999) to conclude that higher HbA1c levels were associated with increased P300 latency and the same was generally true across group mean averages in the present study. Interestingly, Alverenga et al. (2005), who used plasma glucose measures (which are immediate measures unlike the 3-month HbA1c), noted that hypoglycemic blood glucose measures were associated with increased latency. Based on the review of literature, it is possible that the immediate physiologic effects of hypoglycemia would temporarily cause poorer cognitive processing and thereby increase P300 latency while the extended long term effects of poorly managed blood glucose levels, including regular swings between hypo- and hyper-glycemia, may permanently damage the neural system and thereby reduce cognitive processing speed and memory capacity.

It is notable that the covariate hearing did not significantly affect the P300 latency outcome measure as hearing loss has previously been associated with increased P300 latencies (Oates et al., 2002). Oates et al., 2002 demonstrated that even mild differences in hearing loss were reflected in P300 measured conducted at suprathreshold levels. This is likely explained by the normal hearing entry criteria of the study and the fact that differences in hearing were not very vast across subjects.

P300 amplitude. P300 amplitude is the magnitude of the response reflecting the strength of the neural firing rate and the size of the neural population that is recruited in the response

(Oates et al., 2002). In the present study there was a stark contrast between the two categorization methods regarding the P300 amplitude. In the ADA categorization method, there was a significant main effect of DM on P300 amplitude as well as significant relationships between the covariates age and hearing to P300 amplitude. However, using the insulin dependence categorization model, there was no effect of insulin dependence nor were the covariates age and hearing significantly related to P300 amplitude. The largest mean amplitude was found within the prediabetic group.

Vanhanen et al. (1996) and Alvarenga et al. (2005) reported general, not statistically significant, decreases in P300 amplitudes among diabetics. The same general trend is true in the present study. Especially considering that the statistical significance would likely be erased without the prediabetic group. Researchers have explained this decrease in amplitude to represent decreasing cognitive abilities due to the long-term detrimental effects of DM that may appear as accelerated aging (Cooray et al., 2008).

Remarkably, there was a significant increase in amplitude among prediabetics after controlling for age in the ADA category groups. This is especially interesting as this subgroup represented an older mean age than any other subgroup which should have been associated with less intense P300 amplitude (Cooray et al., 2008). A similar result has never before been reported in the literature and no one has ever suggested anything regarding the potential for increased glucose levels among non-diabetics to increase neural activity. It is known that the brain and body react physiologically differently to increases and decreases in glucose levels in the early stages of DM while failing to react to these changes later on in the disease process as the brain begins to habituate to the regular changes in glucose levels (Desouza et al., 2010; Fowler, 2011; Strachan et al., 2003). Though it is simply speculation, perhaps this data suggests

that among individuals without DM but higher HbA1c levels (prediabetics), which infers they are not habituated to the fluctuations in glucose levels associated with DM, there are early homestatic changes due to these changes in glucose levels that make neurons in the brain more sensitive. The relationship between P300 amplitudes and higher HbA1c levels among non-diabetic individuals (prediabetics) bares further exploration in future studies.

It is interesting that there was a difference between the two categorization methods in regards to the influence of age and hearing on P300 amplitude. It was unexpected that neither age nor hearing would influence the P300 measure in the insulin dependence category. Age has repeatedly been associated with decreasing cognitive abilities and as such should be reflected by decreased P300 amplitude (Allen et al., 2004; Cooray et al., 2008; Cosway et al., 2001; Pozzessere et al., 1991; Vanhanen et al., 1996). In addition, hearing loss has been associated with changes P300 amplitudes in previous studies (Oates et al., 2002). Similar to P300 latency measures, perhaps hearing loss did not affect P300 amplitude because the participants had to meet normal hearing criteria prior to entry to the study. Though, that does not explain the reason why the ADA and insulin dependence categories had such different influence on amplitude.

Aim 2 Discussion

The following sections will discuss the results of the audiometric pure-tone tests and speech measures in more detail. Once again, outcomes from both categorization methods will be discussed simultaneously.

Audiometric thresholds. In the present study, there was a difference between the 2 categorization methods in regards to audiometric pure-tone measures. For the ADA categorization methods, there was no significant effect of DM on pure-tone measures after adjusting for age. However, for the insulin dependence category, there was a significant ($p \leq .05$)

main effect of DM on the 250 Hz and standard PTA measures, after adjusting for age. Notably, these frequencies represent ranges involved in speech understanding. There was no main effect on the high and ultra-high PTA measures. As expected, the covariate age was significantly related to all measures of pure-tone audiometry.

Though there was a significant effect of insulin dependence on the 250 Hz and standard PTA measures, the effect size was very small, between 2-5 dB on average (see Table 15). However, this effect size represents an approximate 15-year difference in this model. Figure 9, constructed based on figures from the GLM, represents the predicted standard PTA based on age and insulin dependence status. Within this model, a 35-year old IDDM participant has the same standard PTA threshold as an approximately 50-year old non-diabetic participant. This is similar to the theory that DM contributed to accelerated presbycusis or age-related hearing loss by accelerating presbycusic physiologic changes to the cochlea which has been proposed by other past researchers (Frisina et al., 2006).

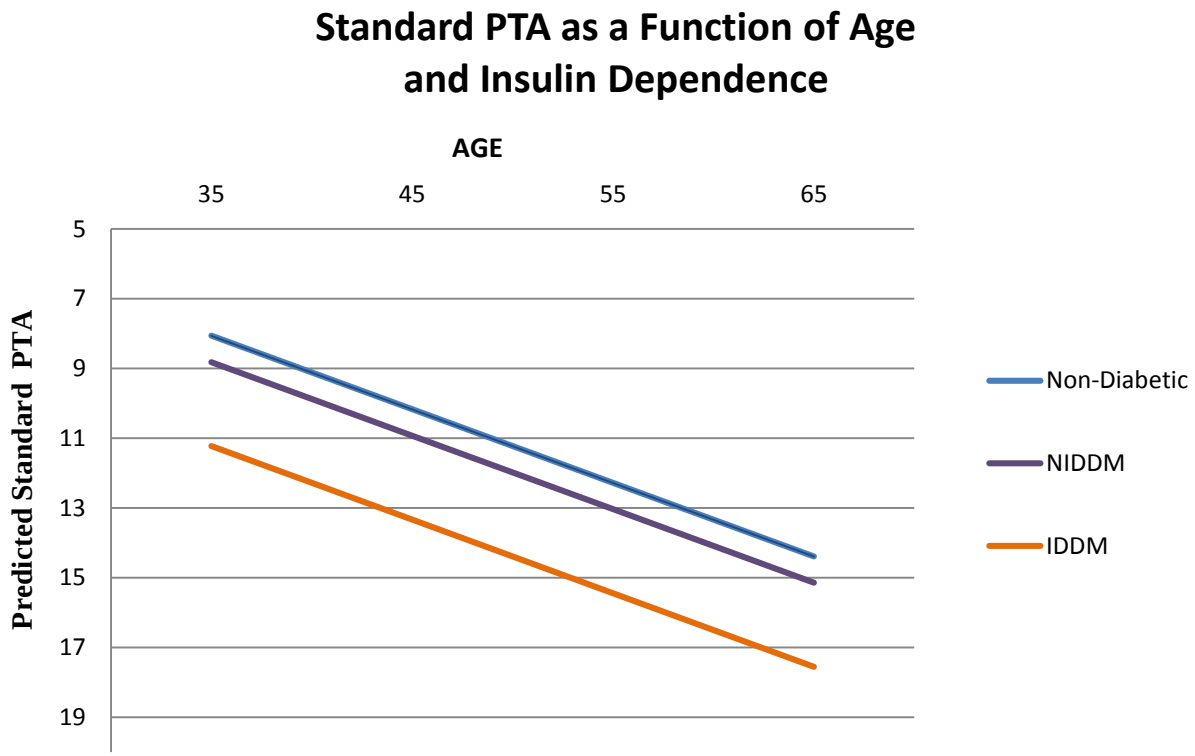

Figure 9. Predicted standard PTA given age and insulin dependence. Using effect sizes from the GLM model, standard PTAs are predicted by age and insulin dependence status. The IDDM group has the poorest scores and represent an approximate 15 year age difference between groups

Interestingly, the areas of significant differences, given age, in pure tones among the insulin dependence category were seen in the low- and mid-frequency regions (250, 500, 1000, and 2000 Hz) while no significant differences were seen in the higher frequencies (3000, 4000, 6000, 8000, 10000, 12500, and 14000 Hz). This represents an agreement with some of the studies and a contrast with other studies in the literature and speaks to a fundamental question within the diabetic and hearing literature whereby there does not seem to be a consensus on the affected frequency region. Several studies have found a low-frequency effect of DM on pure-tone audiometry (Frisina et al., 2006; Ma et al., 1998). Conversely, more have reported the stronger effect of DM on pure-tone measures in the higher frequencies (Agrawal et al., 2009;

Bainbridge et al., 2008; Diaz de Leon-Morales et al., 2005; Uchida, Sugiura, Ando, Nakashima, & Shimokata, 2010; Vaughan et al., 2007). Still, some authors have reported an effect across all frequencies or multiple frequency regions (Austin et al., 2009; Kurt et al., 2002). These differences in results are likely accounted for due to the fact that some studies were limited by older populations which made it difficult to differentiate the effects of DM from the effects of presbycusis while other studies simply did not adjust for age. Moreover, it is possible that DM affects all frequencies but the difference is sometimes evident in lower frequencies because the effect size of presbycusis is larger than that of DM thereby masking DM-related effects in some cases (Frisina et al., 2006).

Low-frequency hearing loss has been proposed as an expression of poor cochlear blood supply associated with strial vascularis atrophy (Schuknecht & Gacek,1993; Schuknecht et al., 1974). As discussed in the literature review section of this document, there are several possible pathogenic-induced changes by DM that could cause and potentiate hearing loss; including, microangiopathic changes to the cochlea, which would impact cochlear blood flow. Multiple human temporal bone studies have revealed significant basement membrane thickening of capillaries of the strial vascularis in addition to atrophy of the stria vascularis area (Fukushima et al., 2006; Wackym & Linthicum, 1986). Moreover, Makishima and Tanaka (1971) reported vascular stenosis of capillaries in the stria vascularis. Similar findings have been found in diabetic animal models (Rust, Prazma, Triana, Michaelis, & Pillsbury, 1992). These microangiopathic changes to the stria vascularis could alter cochlear homeostasis as the within the endolymph and increase free radicals within the system leading to changes in hair cell transduction and possible hair cell death (Frisina et al., 2006).

Speech recognition tests. In both the ADA categorization method and the insulin dependence categorization method, there was no significant main effect of DM or cognition (based on the DSS score) on any of the 3 measures of speech understanding while the covariate age was significantly related to each of these measures. Interestingly, for the QuickSin and 50% time-compressed speech measure, the covariate hearing (based on standard PTA) did not have a significant relationship with measures of speech understanding. However, the effect of hearing was significant on the 60% time-compressed speech measure for both categorization methods. Nonetheless, diabetics generally performed slightly more poorly than non-diabetics across all 3 measures.

Only one study has examined the difference between diabetics and non-diabetics on measures of speech understanding. As noted in the literature review, Frisina et al. (2006) reported significantly poorer scores on the HINT among diabetics. However, the participants of this study were significantly older (mean age = 73) than those from the current study and there was no effort made to statistically control for the effects of age and cognitive ability.

As has been previously noted, both hearing and cognition play a role in speech understanding (Lunner& Sundewall-Thoren, 2007; McCoy, Tun, Cox, Colangelo, Stewart, & Wingfield, 2005; Pkhora-Fuller, 2003). In the present study, diabetics had poorer average speech scores in addition to overall poorer average audiometric and cognitive scores than non-diabetics. Based on the theories above regarding accelerated synergistic effects of DM and aging, it is possible that speech understanding may degrade at a faster rate among diabetics versus non-diabetics especially when all of these covariates, which can be synergistically driven by one another (e.g. DM resulting in poorer pure-tone thresholds) and can be independent of one another (e.g. an outside or genetic influence on pure-tone thresholds), are stacked upon one another.

Similar to cognitive measures, it is possible that increased brain capacity among relatively younger adults may act as a protective agent to the effects of DM (Mu et al., 1999; Pirttilä et al., 1992; Ryan & Geckle, 2000b).

Diabetic Control

In the current study, the diabetic group (ADA category) had a mean HbA1c of 7.74% and a mean duration of disease of 8.33 years. As noted in the literature review, NIDDM and IDDM may be used to define well-controlled DM (NIDDM) and poorly-controlled DM (IDDM) based on the need to manage DM with insulin rather than exercise and diet. In the present study, disease duration and HbA1c levels reflect this notion whereas the NIDDM and IDDM groups straddle diabetic group in terms of these two measures with the NIDDM group representing the less severe measurements and the IDDM group representing the more severe measurements. The NIDDM group had a mean HbA1c of 6.81% and a mean duration of disease of 5.19 years while the IDDM group had a mean HbA1c of 8.53% and a mean duration of disease of 10.96 years.

Interestingly, throughout outcome measures in the current study the NIDDM group had, on average, better mean audiometric and cognitive measures than the diabetic group while the IDDM group has, on average, poorer mean audiometric and cognitive measures than the diabetic group. This was true for the DSS and LNS cognitive behavioral measures, P300 latency and amplitude, all pure-tone measures, and the QuickSIN measures, which covers the majority of outcomes within the current study. From this result, one might suggest that better managed DM may lead to better long-term outcomes and slower declines in measure of audition and cognition.

Clinical Relevance

Though the effect of DM was not statistically significant for many measures and for those that it was, the effect size is small, it may be beneficial for clinicians to consider DM when

creating individualized audiologic monitoring and management plans for patients. DM creates a complicated and complex clinical picture as it seems to generally contribute to measures of audition and cognition among this group of relatively younger adults. Figures 6, 7, and 9 demonstrate the age effect between diabetics and non-diabetics on measures of audition and cognition. Clinicians may take this into account and monitor hearing loss among diabetics, even those with a slight or mild hearing loss, on an annual basis to prevent unchecked acceleration of pesbycusis into a threshold range that impacts daily communication.

In addition, literature reveals a significant effect of DM on cognition while the present study suggests a general but not significant effect. Furthermore, it is known there is a link between hearing loss and cognitive decline that is likely due to isolation caused by hearing loss (Lin, Metter, O'Brien, Resnick, Zonderman, & Ferrucci, 2011; Wingfield, Tun, & McCoy, 2005). Diabetics may experience a compounded effect of hearing loss and cognitive decline due to the cascade of physiologic changes invoked by the disease. Clinicians should specifically consider referrals for diabetics when cognitive decline is suspected and should routinely evaluate speech understanding to monitor the combined effect of cognitive decline and hearing loss on communication.

Moreover, throughout the study, more well-controlled diabetics (represented by the NIDDM group) had better audiometric thresholds and cognitive behavioral scores than less well-controlled diabetics (represented by the IDDM group). Perhaps this is evidence that better management of DM can lead to improved long-term outcomes and less drastic changes in the auditory and cognitive systems.

Lastly, clinicians should take into account the potential for an increased rate of cognitive degradation and potential for increased deterioration of speech recognition measures among

diabetics when choosing long-term hearing loss management among diabetics with hearing loss that warrants intervention. Perhaps more aggressive aural rehabilitation may help counter these declines and improve and sustain long-term amplification usage. The potential for both vision (diabetic retinopathy) and hearing sensory system losses must also be taken into account.

Overall, the present study may contribute to creating a better patient profile and allow clinicians to better develop audiologic intervention plans tailored to each individual patient.

Limitations

The present study was limited to a Veteran population with prior military experience and noise exposure. This created a situation where normal hearing accounted for a noise-notch among participants, likely confounding the effects for pure-tone audiometry at higher frequencies associated with noise damage (3000, 4000, and 6000 Hz). It is very possible that DM affects the entire cochlea and the history of noise exposure confounded this phenomenon. In addition, due to the nature of the Veteran population, the current study included very few women and no children or adolescents. This overwhelming male population with a very specific occupational history in the current study makes applying these results to the general population difficult and unethical.

Furthermore, the organization of participants in the present document created a situation where the number of participants in each subgroup was unequal. Recruiting more participants for each of the subgroups to create more equal numbers and equal mean ages between groups would yield potentially better results.

Future Directions

Longitudinal results will offer a more specific view into the decline and association in audiometric thresholds and cognitive tests among diabetics. This information will make it possible to also determine the effect of well-controlled diabetes on these measures.

The differences in P300 amplitude among prediabetics warrants further investigation. The potential for changes in blood glucose level to affect neural firing rates associated with this measure should be measured in a prediabetic population based on HbA1c and perhaps in a non-diabetic population with elevated plasma glucose levels.

Lastly, as previously noted, the current study is part of a larger longitudinal study which measured several other areas of peripheral and central auditory function (e.g. otoacoustic emissions and auditory brainstem response). These measures, once fully analyzed, may give more insight into the specific effects of DM on the auditory system.

Summary

Type 2 DM is a metabolic disease characterized by the body's inability to secrete and utilize the hormone insulin, which results in hyper- and hypoglycemia, that affects millions of Americans and is projected to increasingly affect populations worldwide, reaching over 30 million Americans by 2030 (ADA, 2011; CDC, 2011; WHO, 2013). Based on current literature, the auditory and cognitive systems are not spared from the negative physiologic consequences of type 2 DM (Kodl & Seaquist, 2008; Fowler, 2011; Fowler & Jones, 1999; Frisina et al, 2006). Moreover, it is known that insults to either of these systems can interact to cause and exacerbate speech comprehension and communication difficulties (Lunner & Sundwall-Thoren, 2007; McCoy et al., 2005; Pkhora-Fuller, 2003). The current body of literature has not fully explored

and described the specific deficits to the auditory system propagated by Type 2 DM and, moreover, has not examined the interaction and impact of auditory and cognitive deficits on communication and speech recognition among Type 2 diabetics. Further, the current body of literature has not fully investigated many of these concepts in a relatively younger adult population and many studies have failed to control for the effect of age and other confounding covariates. A longitudinal cross-sectional study of normal hearing diabetics and non-diabetics was designed to explore the influence of Type 2 DM on the aforementioned systems and, eventually, describe the course of auditory system deficits associated with Type 2 DM. The purpose of this thesis was to report the baseline measures investigating the influence of Type 2 DM on tests of cognitive and audiologic functions among Veterans, including 2 neurocognitive behavioral tests, the electrophysiological P300 measure, pure-tone audiometric thresholds from 250-14000 Hz, and 3 speech recognition tests.

Given age, diabetics had significantly elevated pure-tone thresholds in the low and mid-frequency regions compared to non-diabetics. Markedly, the IDDM group, which had the highest HbA1c measures and longest duration of disease, had the most markedly elevated pure-tone thresholds. In addition, though not statistically significant, diabetics had elevated pure-tone thresholds across all PTAs, poorer scores on measures of speech recognition, poorer neurocognitive behavior test scores, and more latent and less intense P300 measures versus their non-diabetic counterparts. Generally, these differences were more noticeable between the IDDM group and the non-diabetic controls, whereby the IDDM group commonly had the poorest outcomes.

These results indicate some very subtle significant differences and some general differences regarding hearing, cognition, and speech recognition between non-diabetics and

diabetics, especially for a less-well controlled population (e.g. IDDM). Specifically, it is noted that while the effect sizes are small, they often represent a noteworthy aging effect within the models in this paper. Within these models, diabetics often represent audiologic thresholds and cognitive test scores indicative of a person 10-15 years older than their non-diabetic peers. It is almost as if the diabetic system is aging more rapidly than that of a non-diabetic, resulting in poorer outcomes. As it is known that cognition and hearing loss can impact speech recognition and synergistically affect one another; perhaps some thought must be given by audiologic clinicians to monitor diabetics more closely and take DM into account to tailor and individualize specific decisions regarding their patient's audiologic rehabilitation.

APPENDIX A

Table A1

Univariate Statistics Results for ADA Category

	F-statistic	*DF (Between-Groups)*	*DF (Within-Groups)*	*P-Value*	*ω*
		Behavioral Cognitive Measure			
DSS	3.448	2	127	0.035	0.19
LNS	2.138	2	127	0.122	0.13
		Electrophysiologic Measures			
P300 Latency	2.138	2	98	0.123	0.15
P300 Amplitude	2.331	2	98	0.103	0.16
		Audiometric Data			
250 Hz	3.830	2	127	0.024	0.20
Standard PTA	3.236	2	127	0.043	0.18
High PTA	2.152	2	127	0.120	0.13
Ultra High PTA	3.196	2	126	0.044	0.18
		Speech Recognition Tests			
QuickSIN	1.706^{0}	2^{0}	N/A	0.426^{0}	N/A
TCS 50%	$.903^{0}$	2^{0}	N/A	0.637^{0}	N/A
TCS 60%	2.933^{0}	2^{0}	N/A	0.231^{0}	N/A

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing; 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; All pure-tone averages reported in dB HL; P300 Latency is measured in msec; P300 Duration is measured in μV; ^{0} = Kruskal-Wallis Non-parametric (H-Statistic)

Table A2

Univariate Statistics Results for Insulin Dependence Category

	F-statistic	*DF (Between-Groups)*	*DF (Within-Groups)*	*P-Value*	*ω*
		Behavioral Cognitive Measure			
DSS	4.589	2	104	0.012	0.31
LNS	2.866	2	104	0.061	0.18
		Electrophysiologic Measures			
P300 Latency	0.745	2	78	0.478	0.08
P300 Amplitude	0.667	2	78	0.516	0.09
		Audiometric Data			
250 Hz	6.754	2	104	0.002	0.31
Standard PTA	5.873	2	104	0.028	0.05
High PTA	1.173	2	104	0.314	0.06
Ultra High PTA	3.713	2	104	0.028	0.05
		Speech Recognition Tests			
QuickSIN	4.630^{0}	2^{0}	N/A	0.099^{0}	N/A
TCS 50%	2.715^{0}	2^{0}	N/A	0.257^{0}	N/A
TCS 60%	2.318^{0}	2^{0}	N/A	0.314^{0}	N/A

Note. DSS = Digit Symbol Substitution; LNS = Letter-Number Sequencing; 250 Hz = best ear 250 Hz measure; Standard PTA = best ear pure-tone average at 500, 1000, and 2000 Hz; High PTA = best ear pure-tone average at 3000, 4000, 6000 and 8000 Hz; Ultra High PTA = best ear pure-tone average at 10000, 12500, and 14000 Hz; TCS 50% = 50% time-compressed speech; TCS 60% = 60% time-compressed speech; All pure-tone averages reported in dB HL; P300 Latency is measured in msec; P300 Duration is measured in μV; ^{0} = Kruskal-Wallis Non-parametric (H-Statistic)

APPENDIX B

Institutional Review Board #1
Portland VA Medical Center
Portland, OR

IRB APPROVAL - Notification

Date: June 20, 2013
From: Nickie S. Pierce
Investigator: Dawn L. Konrad-Martin, Ph.D.
Protocol: *Longitudinal Changes in Auditory Function Among Veterans with Diabetes (Co-PI: Marilyn Dille, Ph.D.) (#05-1910)
Sponsor: 9022 = VA - Rehabilitation R&D • Admin: 02 = VA
ID: 02631 Prom#: 0006 Protocol#: C7455R

The following items were reviewed and approved through Expedited Review:

- Memo - add Nick Reed (05/28/2013; 05/28/2013)
- Project Revision/Amendment Form - add Nick Reed (05/28/2013; 05/28/2013 rcvd)
- Research Personnel Change Form - Add Nick Reed (05/23/2013; 05/29/2013 rcvd)
- Scope of Work - IRQ Appendix L - Nick Reed (05/23/2013; 05/28/2013 rcvd)

Expedited Approval [Expedited under Federal Regulation: 45 CFR 46.110(b)(2) / VA Regulation: 38 CFR 16.110(b)(2)] was granted on 06/20/2013. The reviewer was John C. McDermott, Ph.D. This Expedited review will be reported to the fully convened Institutional Review Board #1 on 07/03/2013.

The Portland VAMC IRB is not connected with, has no authority over, and is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. Separate consent forms, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

Portland VA Medical Center Institutional Review Board

IRQ Appendix L – Scope of Work

For Office Use Only
MIRB No: _____

Project Title: Longitudinal Changes in Auditory Function Among Veterans with Diabetes

Name of Individual/Employee: Nicholas Reed, BA

Position on Study: Student Intern
(e.g., co-investigator, responsible clinician, research nurse, research coordinator, etc.)

- Is the individual a student or trainee (e.g., resident or fellow) working on the research to fulfill educational requirements? Yes ☒ No ☐
  If Yes, name of educational institution: Towson University

- Has the individual earned a new degree or obtained licensure or certification since the time they initially started working on PVAMC research? Yes ☐ No ☐ N/A – first study ☐
  If Yes, please submit a revised Education Verification Form.

Name of Principal Investigator:

This form should be completed by the principal investigator for each individual (including the PI) working on the PVAMC portion of the study identified on this form. ***If the study includes another research site in addition to the PVAMC, the answers below should only apply to those procedures conducted on VA time.***

PROCEDURES:

	Yes	No
1. Screens patients to determine study eligibility criteria by reviewing patient medical information or interviewing subjects.	☒	☐
2. Is knowledgeable of the informed consent process and is authorized to obtain informed consent from research subjects for this study.	☐	☒
3. Administers questionnaires or conducts mental status or psychosocial exams.	☒	☐
4. Interacts with subjects by performing physical examinations or procedures. If yes, describe the exam to be performed and list all procedures or attach pages from protocol that describe exams and/or procedures: **Audiology exam for research study, includes the following tests: Puretone air and bone; immittance; filtered speech; Auditory Brainstem (ABR); Otoacoustic Emissions (OAE); Event related Potentials (P300); and questionnaires.**	☒	☐
5. Provides education and instruction to subjects or relatives regarding details of study and, if applicable, study medication, including use, administration, storage, side effects and reporting adverse drug reactions to study site.	☒	☐
6. Prescribes and renews study medication. If yes, submit a Prescription Authorization Form for this individual. The form can be found at http://www.portland.va.gov/research/documents/irb/prescription-authorization.doc	☐	☒
7. Has final responsibility for reviewing laboratory data and other entries in the medical record for the purpose of identifying adverse events.	☐	☒
8. Performs venipuncture. If yes, describe training and steps taken by PI to ensure competency:	☐	☒
9. Places intravenous (IV) lines and administers IV treatment. If yes, describe training and steps taken by PI to ensure competency:	☐	☒

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CURRICULUM VITA

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EDUCATION

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EXPERIENCE

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Feb 2013- May 2013	**Intern, ENTAA Care, Audiology** *Colombia and Glen Bernie, MD (ENT/Audiology Practice)*
Feb 2012- Dec 2012	**On-Campus Clinician, Towson University Audiology Clinic** *Towson, MD (University Clinic)*
Aug 2011- May 2012	**Research Assistant to Dr. Stephanie Nagle, Towson University** *Towson, MD (University Lab)*
Aug 2010 - Aug 2011	**Coordinator, Jobs for America's Graduates** *Indianapolis, IN*
May 2008 - Aug 2010	**Director of Expansion, Phi Kappa Psi Fraternity Inc. HQ** *Indianapolis, IN*

PUBLICATIONS & PRESENTATIONS

Hammond, T., & **Reed, N.** (2014). Advocate for your future as an audiologist: An interview with the academy's capitol hill office. *Audiology Today*, *26*(2), 68-70.

Reed, N.S., Dille, M., Reavis, K, McDermott, D., Gordon, J., Austin, D., and Konrad-Martin, D. (2013) *The Effect of Diabetes on Measures of Auditory and Cognitive Function.* Poster presented at National Center for Rehabilitative Auditory Research Bi-Annual Conference, Portland, OR, September 2013.

Reed, N.S., Reavis, K., Dille, M., McDermott, D., Gordon, J., Austin, D., and Konrad-Martin, D. (2014) *Auditory and Cognitive Effects of Diabetes: Influence of Disease Severity.* Poster presented at American Auditory Society Conference, Scottsdale, AR, March 2014.

Reed, N. S. (2014). *Control Your Career Path; Student Advocacy*. Presentation to be held at Student Summit at AudiologyNow, Orlando, FL, March 2014. (Invited Speaker)

RECENT HONORS AND AWARDS

• Audiology Research Travel Scholarship Recipient • Assoc. of Schools of Allied Health Professions Scholarship of Excellence • Towson Alumni Association Fellowship • National Institutes of Health Research Fellow • Towson University Academic Scholarship

PROFESSIONAL ORGANIZATION AFFILIATION & SERVICE

• American Tinnitus Association • Maryland Academy of Audiology, *Student Member* • American Academy of Audiology (*Current Member of National Student Advocacy Committee)* • Student Academy of Audiology, Towson University Chapter, *Member (Former President)* •