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Diabetes-associated Changes in Cortical Auditory Evoked Potentials in Relation to Normal Aging

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Abstract

OBJECTIVES—(1) Characterize the influence of type 2 diabetes mellitus (DM) on cortical auditory evoked potentials (CAEPs) separate from the effects of normal aging; and (2) determine if the disease-related effects are modified by insulin dependence.

DESIGN—A cross-sectional study was conducted in a large cohort of Veterans to investigate the relationships among type 2 DM, age and CAEPs in randomly selected participants with (N=108) and without (N=114) the disease and who had no more than a moderate hearing loss. Participants with DM were classified as insulin-dependent (IDDM, N=47) or non-insulin-dependent (NIDDM, N=61). Other DM measures included concurrent serum glucose, HbA1c and duration of disease. CAEPs were evoked using a passive homogeneous paradigm (single repeating stimulus) by supra-threshold tones presented to the right ear, left ear, or both ears. Outcome measures were adjusted for the pure tone threshold average (PTA) for frequencies of 0.5, 1, and 2 kHz and analyzed for differences in age effects between participant groups using multiple regression.

RESULTS—There is little variation across test ear conditions (left, right, binaural) on any CAEP peak in any of the groups. Among no-DM controls, P2 latency increases about 9 ms per decade of life. DM is associated with an additional delay in the P2 latency of 7 and 9 ms for the IDDM and NIDDM groups, respectively. Moreover, the slope of the function relating P2 latency with age is similar across participant groups and thus the DM effect appears constant across age. Effects on N1 latency are considerably weaker, with age effects of less than 4 ms per decade across all groups, and DM effects of only 2 (IDDM) or 3 ms (NIDDM). In the NIDDM group, the slope relating N1 latency to age is steeper relative to that observed for the no-DM group, providing some evidence of accelerated “aging” for this CAEP peak. DM does not substantially reduce N1-P2

amplitude and age relationships with N1-P2 amplitude are effectively absent. There is no association between PTA at .5, 1, and 2 kHz and any aspect of CAEPs in this cohort.

CONCLUSIONS—In a large cohort of Veterans, we found that type 2 DM is associated with prolonged N1 and P2 latencies regardless of whether insulin is required to manage the disease and independent of peripheral hearing thresholds. The DM-related effects on CAEP latencies are three fold greater for P2 compared with N1, and there is little support that at the cortical level, IDDM participants had poorer responses compared with NIDDM participants, although their responses were more variable. Overall, these results indicate that DM is associated with slowed pre-attentive neural conduction. Moreover, the observed 7–9 ms P2 latency delay due to DM is substantial compared with normal age changes in P2, which are 9 ms per decade of life in this cohort. Results also suggest that whereas N1 latency changes with age are more pronounced among individuals with DM versus without DM, there was no evidence for more rapid aging of P2 among patients with DM. Thus the damage responsible for the major DM-related differences may occur early in the DM disease process. These cross-sectional results should be verified using a longitudinal study design.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder resulting from either insulin deficiency (type 1 DM) or reduced insulin production coupled with resistance (type 2 DM). DM can produce devastating vascular and neurological complications. Excess glucose metabolism, the fundamental disease process of type 2 DM-related changes in the body, leads to macrovascular disease (heart disease, stroke, high blood pressure), microvascular disease (kidney disease, blindness, hearing loss), neuropathy (autonomic and peripheral, declines in cognitive function), and loss of limbs. A better understanding of the health impacts of the disease is critical as the prevalence of DM is nearing epidemic levels, affecting one in ten adults in the U.S. and one in four to five adults over age 60 (<http://diabetes.niddk.nih.gov/DM/PUBS/statistics/#people>). Type 2 accounts for 90% of DM (WHO, 1999) and compared with type 1 has higher associated risks of macrovascular and microvascular complications (Constantino et al. 2013; Kershner et al. 2006; Maahs et al. 2007; Rodriguez et al. 2010).

Accumulating evidence suggests that DM may cause complications of the auditory system from the cochlea to cortex, which would not be surprising given its pathological effects on the body's microvascular and nervous systems. Effects of DM on hearing sensitivity have been widely reported. We and others have found that those with DM have poorer hearing than control participants without DM and that this difference in hearing is most apparent among those under the age of 50 – 60 years, before age-related changes begin to dominate (Frisina et al. 2006; Vaughn et al. 2005; Bainbridge et al. 2008; Austin et al. 2009; Bainbridge et al. 2011; Konrad-Martin et al. 2015; Horikawa et al. 2013; Akinpelu et al. 2014a). Combining data across multiple studies, a recent meta-analysis estimates the odds of having a hearing loss of 25 dB HL or greater among individuals with type 2 DM is roughly twice that observed among controls (OR 1.91; 95% confidence interval [CI] 1.47–2.49) (Akinpelu et al. 2014a). Pooled data further indicate that the risk of hearing loss is increased for hospital-based populations with more severe DM compared with DM in the general

population (Horikawa et al. 2013). Effects of DM have also been shown on the auditory brainstem response, ABR (Parving et al. 1990; Bayazit et al. 2000; Durmus et al. 2004; Diaz de Leon-Morales et al. 2005; Vaughn et al. 2007b; Konrad-Martin et al. 2010; Akinpelu et al. 2014a). Konrad-Martin et al. (2010) found, primarily among younger patients (< 50 years) dependent on insulin to manage their DM (IDDM participants), lower amplitude of ABR wave V, longer latency of waves III and V, and prolonged I-V interpeak latency interval compared with control participants, indicative of central auditory system effects. This younger group also had poorer hearing than the controls, although individuals with severe hearing loss were excluded from the study and hearing sensitivity was controlled in the analysis.

Significant effects of DM on pure tone thresholds and central ABR components are found more often than not upon investigation, however, there is substantial between-study heterogeneity in the findings (hearing and ABR: Akinpelu et al., 2014a; hearing: Horikawa et al. 2013; Konrad-Martin et al. 2015). There are a number of possible reasons for this. Some studies define diabetes status based on self-report, do not differentiate between type 1 and type 2, or use samples of individuals with mild disease or who are older and may suffer from more dominant aging effects. Additional studies are needed to clarify the magnitude of DM effects along the entire auditory pathway, the progression with age and disease duration, dependence on DM severity, and impact of glycemic control.

A non-behavioral approach for examining how disease processes and normal aging alter the auditory signal reaching the human cortex involves the measurement of cortical auditory-evoked potentials (CAEPs), which originate within the thalamo-cortical segment of the auditory pathway and provide a neural encoding index of the acoustic environment. More specifically, CAEPs represent the synchronous postsynaptic potentials of large groups of cortical neurons, and their latencies and amplitudes are altered by the number and synchrony of contributing neural units activated by the stimulus (Eggermont 2007). Amplitude is measured in microvolts and interpreted as representing the response strength; whereas, latency is measured in milliseconds after the stimulus onset and provides an indication of the amount of time it takes for sound to be encoded at the cortex. Relatively abrupt sound onsets or changes in frequency, level and rate are all coded by changes in latency and/or amplitude of the response complex or its threshold (Hansen and Hillyard 1984; Naatanen & Picton 1987). The CAEP has been used to estimate hearing sensitivity (Martin et al. 2008) and higher order processing including hearing in background noise and effects of signal-to-noise ratio on speech understanding (Billings et al. 2015; Billings et al. 2013; Bennett et al. 2012).

Few reports have investigated the effects of DM on CAEPs and results were obtained in small participant samples without accounting for potential age and hearing differences between groups, which could explain discrepancies in the findings. Donald et al. (1980) examined CAEPs in older adults with and without DM, but found no difference in the N1 or P2 latency or P2 amplitude between groups. More recently, Manjarrez et al. (2007) assessed N1 and P2 latencies and the N1-P2 amplitude-level slope obtained using responses elicited by clicks in normal-hearing women with or without type 2 DM. They found significantly longer N1 and P2 latencies at all intensities in the diabetic group and steeper N1-P2 amplitude-level slopes. These findings were interpreted as suggesting delayed cortical

encoding of auditory stimuli and a change in the inhibitory-excitatory balance with DM. The results represent initial evidence that pre-attentive auditory effects may be occurring at the level of the cortex with DM, at least among females. Notably, the women with DM all had good diabetic control (glycated hemoglobin, HbA1c, <7%) and no history of cardiovascular complications of the disease or neurological events.

Macrovascular changes, microvascular changes, oxidative stress and homeostatic insulin changes have been implicated as possible biological mechanisms responsible for the DM-related auditory and cortical/cognitive dysfunction (Aimoni et al. 2009; et al. 2006; Bainbridge et al. 2011; Kodl & Seaquist 2008). DM induces auditory and cerebral vascular injury similar to that caused by the reduced cerebral blood flow that accompanies aging. Accordingly, effects of DM on the ear and brain have been described in the literature as “accelerated aging” since damage from the disease is similar to that observed in the elderly though found at younger ages in those with DM (Biessels et al. 2006; Kodl & Seaquist 2008; Akinpelu et al. 2014b). In addition to effects attributable to chronic hyperglycemia, it is also possible that severe hypoglycemic episodes could contribute to auditory neural deficits as suggested by cardiac conduction changes and by peripheral neuropathy studies in animals (Gruden 2012, Jensen 2014).

In this cross-sectional, observational cohort study, we investigate DM-related changes in CAEPs among the same group of Veterans for whom we have previously published pure tone threshold (Austin et al. 2009) and ABR results (Konrad-Martin et al. 2010). Here we chose to focus on estimating the difference in the CAEP decline over time among Veterans with DM from the trajectory associated with normal age-related changes. Different theoretical models of the interaction between DM and aging can induce apparent accelerated aging. A simple representation of some of these models is shown in Figure 1. “Auditory dysfunction” is represented on the y-axis and age on the x-axis. Normal auditory senescence is shown as the solid black line. The gray lines show different aging trajectories following the onset of DM, indicated by the arrow on the x-axis. The dashed gray line represents smoothly accelerated auditory senescence compared to the normal trajectory. The solid gray line shows an initial acceleration, perhaps associated with pre-diagnostic period of DM, followed by a path of auditory aging that is parallel to normal senescence. This particular model may adequately represent effectively controlled diabetes with medication, exercise, and diet, despite some initial damage caused by early manifestations of DM. A combination of these two models is shown by the dotted gray curve, where both an initial ‘jump’ in dysfunction followed by accelerated senescence occurs, perhaps representing more severe or poorly controlled DM. The reference line on the vertical axis identifies the threshold for clinically recognized auditory dysfunction. The age at which a particular curve crosses the line identifies the age at onset of clinically relevant auditory dysfunction. Each model of DM shows an earlier onset compared to normal aging, though the process by which that is achieved is currently unclear.

Previous studies measuring auditory senescence with the N1-P2 response vary markedly in test paradigms, sampling criteria, and results. Most found that N1 and/or P2 latencies increased with increasing age (Papancoulaou et al. 1984; Vanhanen et al. 1996; Tremblay et al. 2004; Harris et al. 2007; Harris et al. 2008; Lijffijt et al. 2009; Kim et al. 2012) though

some did not (Spink et al. 1979; Laffont et al. 1989). N1 and/or P2 amplitude changes with age were perhaps even more variable. Papanicolaou et al. (1984), Tremblay et al. (2004), and Goodin (1978) found amplitudes to decrease with increasing age while Pfefferbaum et al. (1980) Kim et al. (Kim et al. 2012) and Polich (1997) found significant increases or trends toward larger amplitudes with increasing age. Finally, Harris et al. (2008) Laffont et al. (1989) and Spink et al. (1979) found no effects of age. Most studies of auditory senescence in general, and of N1-P2 in particular, are afflicted by small samples and inadequate control for hearing loss, which typically accompanies aging and can confound estimated aging effects on N1-P2. This is especially problematic because effects of age are reported as 'present' or 'absent' dictated by p-values contrasting participants of different ages. P-values are highly sensitive to the statistical model that is used, and many important assumptions are either unevaluated or cannot be evaluated, leaving investigators little concrete information on which to base any refinement of senescence models such as shown in Figure 1.

Aims of this report are to quantify the effect of type 2 DM on the age-related trajectory of N1 and P2 peaks and, in keeping with our prior reports in this cohort, to investigate the extent to which insulin use among diabetics impacts the association. From past analyses, we have found insulin use to be a reasonably good indicator of DM severity, effectively capturing metrics that include longer duration and greater prevalence of complications (Austin et al. 2009; Konrad-Martin et al. 2010). Importantly, although this cohort of Veterans was selected to have relatively good hearing, results are presented after statistically adjusting for any hearing differences in the sample using a multiple regression approach. This allows us to focus on neuronal changes beyond those which might be associated with the known peripheral hearing impacts of the disease. Further, here we focus on the magnitude of age and DM effect sizes, which might be useful for determining whether any additional cortical change from DM is meaningful for diabetic patients from the standpoint that the change is large relative to normal senescence. We use a Bayesian analysis to estimate the range of effect sizes within which we are nearly certain the true effect lies and an estimate of the probability that a given CAEP peak is longer (or shorter), smaller (or larger) compared with the corresponding metric in non-diabetic participants. Finally, outcome measures were analyzed for differences in aging effects between participant groups to determine whether or not the data conform to any of the senescence models proposed in Figure 1. We hypothesized that CAEPs among individuals with DM would resemble those obtained in individuals without DM at a comparatively older age. We further expected that the effects of DM would be more pronounced among individuals with IDDM compared with NIDDM.

PARTICIPANTS AND METHODS

The following report describes CAEPs obtained as part of a large, prospective diabetes study (2006–2009) investigating effects of DM on auditory function. A more detailed description of the recruitment process and standard audiometric tests performed can be found elsewhere (Austin et al. 2009).

Participants

Veterans receiving care in the VA Portland Health Care System (VAPORHCS) were eligible for the study. We selected three random samples without replacement of primary care patients with and without DM and with a maximum age of 70, 60, or 50 years. (The upper age limit had to be reduced over the course of the study in order to recruit a range of older, middle aged and younger adults.) These samples were used in a rolling recruitment in which several DM participants were recruited followed by controls that were age- and sex-matched participants, followed by several more DM participants, etc. Exclusions in addition to age included 1) those undergoing treatment for cancer or with diagnosis of multiple sclerosis, dementia or other neurologic diseases, 2) those with communication difficulties that would prevent them from study participation, wearing hearing aids or with a hearing loss in both ears exceeding 40 dB HL at 2 kHz or 70 dB HL at 4 kHz chosen to increase the likelihood of obtaining other evoked responses (ABR), and 3) those with a clinically significant conductive component to their hearing loss (air-bone gap ≥ 15 dB) or evidence of active otitis externa. Additionally, participants scoring 24 or less on the Mini-Mental Status Examination were also excluded (Folstein et al. 1975). Of initially identified eligible patients, nearly 85% either declined (about 83%) or were excluded upon examination (2%) so the remaining 15% of eligible participants represented a mostly self-selected group meeting study criteria. Type 1 DM was uncommon in the parent study because it often presents in childhood or young adulthood and, therefore, most of those with type 1 DM would not be eligible for military service. For the present report, data were evaluated only from individuals with type 2 DM (type 1 DM was an exclusionary criterion). All participants were consented to participate in the study following the guidelines of the VAPORHCS Institutional Review Board (IRB), signed an IRB approved consent form, and were compensated for their time.

The planned analysis was to divide groups based on the presence of DM and for those with DM to further divide participants by insulin use (yes/no). Those patients who used insulin to manage their disease were labeled insulin-dependent DM, IDDM; those who did not were non-insulin-dependent DM, NIDDM.

Procedures

Audiometry—Hearing thresholds were assessed using the modified Hughson-Westlake procedure (Carhart & Jerger, 1959) bilaterally at the octave interval frequencies from 0.25 to 8 kHz and the inter-octave frequencies 3 and 6 kHz by air using Etymotic ER3 (Etymotic Research, Inc., Elk Grove Village, IL.) insert earphones and at the extended high frequencies of 10 kHz, 12.5 kHz, and 14 kHz using Sennheiser HDA-200 headphones (Sennheiser Electronic Corp., Old Lyme, CT.). Bone conduction thresholds were obtained at 0.5, 1, 2 and 4 kHz using a Radioear B71 bone vibrator (Radioear Corp., New Eagle, PA). Admittance testing using a 226-Hz probe and acoustic reflex threshold testing at 0.5, 1 and 2 kHz with the stimulus ipsilaterally and contralaterally was done bilaterally on the same day as CAEP testing.

Acoustic reflex testing, as well as several other measures that were completed on each participant (including speech audiometry, and hearing asymmetries and substantial asymmetries in ABR results not attributable to noise exposure) were used to rule out

retrocochlear disorder. No participant was suspected of having retrocochlear abnormalities based on results of these tests. Data collection for the parent study required 5–7 hours per participant, including breaks. Most other procedures were done on a visit prior to CAEP testing. All auditory testing was completed with participants seated in a double walled booth.

CAEP Calibration and Stimulus—Stimuli for CAEP measures were delivered and responses were differentially recorded using Intelligent Hearing System SmartEP Version 3.95. To elicit CAEPs, a homogenous stimulus paradigm was used in which participants listened to 600 presentations of a tone burst with a center frequency of 0.5 kHz, a duration of 10 ms, presented at a rate of 1.1 per second and at a level of 90 dB peak-peak equivalent SPL (p-pe dB SPL). Using Etymotic ER-3 insert earphones, the stimulus was played to both ears, left and, finally, right ear. Calibration of the stimulus was done using a Bruel and Kjaer (B&K) sound level meter (B&K 2231) with the earphone seated in the B&K 4157 coupler. The electrical output of the toneburst stimulus was displayed on an oscilloscope. The representation of the acoustic waveform was then adjusted to be superimposed on a 3 kHz continuous sine wave in the coupler resulting in a peak-peak equivalent sound pressure level of 90 dB.

Electrode Placement—Skin was prepped prior to electrode placement and responses were recorded using silver/silver chloride scalp electrodes at Fz, Cz, and Pz serving as the active (noninverting) sites. Linked mastoid electrodes served as the reference (inverting) site for the binaural recording and contralateral (to the stimulated ear) mastoid served as reference for the monaural recording. Fpz served as the ground for all recordings. After each collection interval, the participant was evaluated for alertness. Participants were asked to stay alert and awake while visually fixating on a cross on the wall of the test suite. Breaks in testing were given if requested to improve alertness.

Recording Parameters—The recording window consisted of 512 ms pre- and post-stimulus time intervals for a sampling period of 1024 ms. Responses were bandpass filtered from 1–100 Hz and amplified at a gain of 50,000. An artifact rejection threshold was set at or near 80 microvolts (μ V). Prior to testing, each participant was given feedback on relaxation should noise from the participant exceed this window. At the end of two blocks of 300 stimuli, the response was judged to be acceptable or not. If both the N1 and P2 peaks were clearly identified after two blocks of 300 presentations, data collection ceased for that recording parameter. If the peaks were not reasonably consistent reproductions, data collection continued until two suitably reliable peaks were obtained.

Waveform Analysis—Amplitude and latency values for N1 and P2 were determined using the Cz recording electrode (because it shows the maximal evoked response) and analyzed for each ear and participant factor. N1 was defined as the largest negative going peak while P2 was the largest positive peak within a response window of 512 ms. Peak-to-peak amplitudes for both N1 and P2 were calculated from markers placed at each positive and negative peak. That is, N1-P2 amplitude was taken as the measurement in μ V from the peak amplitude of the N1 response to peak amplitude of the P2 response. A peak-to-peak

amplitude measure was used to characterize the overall amplitude change across both peaks. Latency was calculated from the onset of the stimulus to the peaks of N1 and P2. Peaks were scored by one experienced examiner (DM). However, a second experienced examiner (CB) was asked to affirm the scoring decisions on approximately 25% of peaks that proved difficult to score. Both examiners were blinded to DM status or age of participants.

Statistical Approach

In this analysis we characterize 1) the relationship between age and N1-P2 measures and 2) the extent to which DM and insulin dependence modifies these relationships. This characterization is derived from the observed sample of 222 participants' N1 latency, P2 latency, and N1-P2 amplitude (collectively referred to as the CAEP) measured in response to a left ear stimulus, a right ear stimulus, and a binaural stimulus. The number of scorable observations for each stimulus presentation condition (i.e., the data structure) is shown in Table 1.

It was considered important to ensure that the estimated relationship between age and CAEP was not attributable to their mutual association with peripheral hearing sensitivity. The standard approach of estimating adjusted relationships between independent variables (i.e. age) and dependent variables (CAEP latency and amplitude) is regression. If Gaussian residuals are reasonable, and the relationship is adequately described by a straight line, then the approach is the familiar standard linear regression. Easily interpreted estimates of age effects are given by the regression coefficients, which express the change in CAEP magnitude (e.g. N1 latency in ms) per year of life. Similarly, differences in the age effects among DM and control groups are given by differences in the regression coefficients. We further generalize the approach to include responses to stimuli in the left ear, the right ear, and both ears together. Thus the approach is a multivariate response regression analysis.

The N1 latency, P2 latency, and N1-P2 amplitude were modeled separately, but the general model structure is the same for each CAEP peak. Let y_B , y_L , y_R denote the responses to the binaural, left, and right ear stimuli, respectively, given by the i^{th} participant. The multivariate response regression data model for multivariate normal (MVN) data is

$$\begin{pmatrix} y_B \\ y_L \\ y_R \end{pmatrix}_i \sim MVN \left(\begin{pmatrix} \mu_{B,d[i]} + \alpha_{B,d[i]} \cdot Age_i + \mu_{B,d[i]} \cdot PTA_i \\ \mu_{L,d[i]} + \alpha_{L,d[i]} \cdot Age_i + \mu_{L,d[i]} \cdot PTA_i \\ \mu_{R,d[i]} + \alpha_{R,d[i]} \cdot Age_i + \mu_{R,d[i]} \cdot PTA_i \end{pmatrix}, \Sigma \right), \quad (1)$$

where Σ is an unstructured covariance matrix expressing the correlation among responses binaural, left, and right ear stimuli. The μ terms are intercepts, α terms are age effects, and the β terms are PTA effects. For the purposes of this analysis age was centered at 50 years and PTA was centered at 15 dB so that the intercepts μ are the mean latency or amplitude for an arbitrary 50 year old with PTA of 15 dB. The age effects α are expressed as the change in units of the CAEP response (ms for N1 and P2 latencies and μV for N1-P2 amplitude) per year of life. Similarly, the β terms are the change in CAEP response per dB of PTA. The subscripts denote the element of the response vector and the DM group d to which the i^{th}

participant belongs. For instance, $\alpha_{L,not\ diabetic}$ denotes the age effect on the left ear response among non-diabetic participants.

The μ , α , and β terms are modeled as hierarchical random effects such that

$$\begin{aligned}\mu_{B,d}, \mu_{L,d}, \mu_{R,d} &\sim Normal(\mu_d, |\sigma_\mu|), \\ \alpha_{B,d}, \alpha_{L,d}, \alpha_{R,d} &\sim Normal(\alpha_d, |\sigma_\alpha|), \\ \beta_{B,d}, \beta_{L,d}, \beta_{R,d} &\sim Normal(\beta_d, |\sigma_\beta|).\end{aligned}\quad (2)$$

The hyper-parameters μ_d , α_d , and β_d are DM-specific intercepts, age effects, and PTA effects across binaural, left, and right ear stimulus conditions. These are also random effects such that

$$\begin{aligned}\mu_d &\sim Normal(C, |\tau_\mu|), \\ \alpha_d &\sim Normal(0, |\tau_\alpha|), \text{ and} \\ \beta_d &\sim Normal(0, |\tau_\beta|).\end{aligned}\quad (3)$$

We set $C = 110$ ms for N1 latency, 180 ms for P2 latency response, and 5 μ V for N1-P2 amplitude. The $|\tau|$ and $|\sigma|$ are the variance components for the random effects. These describe variability among DM groups and variability among responses to different stimulus conditions within DM groups.

This model is a linear regression of each CAEP response on age and PTA, where the intercept, age, and PTA effects vary among presentation condition and among DM groups recruited into this study. The hierarchical framework facilitates interpretation of these effects at either the ear under test, given by the $\mu_{B,d}$, $\alpha_{B,d}$, $\beta_{B,d}$, $\mu_{L,d}$, $\alpha_{L,d}$, $\beta_{L,d}$, $\mu_{R,d}$, $\alpha_{R,d}$, and $\beta_{R,d}$ or at the DM group level, averaged over stimulus conditions, given by the μ_d , α_d , and β_d . The hierarchical model also offers an intuitively appealing way to handle the problem of multiplicity. The model structure stipulates that the overall effect of age and PTA on each CAEP is effectively characterized by a straight line that is particular to each DM group. Around these overall profiles are different lines associated with each ear stimuli that will be pulled towards the overall profile *unless the data strongly dictate otherwise*. Put another way, we can accept a relatively simple model (the overall line) with reasonably small deviations about it unless particular ear-level stimuli induce considerable departure from the overall line. This approach is more satisfying than post-hoc p-value adjustments such as Bonferroni, which severely reduce statistical power and assume that the individual p-values are independent (Gelman et al. 2012).

This model was fit within a Bayesian framework (Gelman et al. 2014), which facilitates inferences about the regression coefficients. For example, we are 95% certain that the 95% Bayesian confidence interval on the $\alpha_{B,Control}$ parameter contains the true age effect in a population of healthy people without DM. The final ingredient necessary for the Bayesian analysis are the priors on the variance components τ and σ , as well as on the residual

covariance matrix Σ . τ and σ are given Cauchy (0, 25) priors, so that $|\tau|$ and $|\sigma|$ have “half-Cauchy” priors, which are weakly informative over a large range of possible random effects variances (Gelman et al. 2014). Σ is given an inverse-Wishart (4, ω), where ω is a 3×3 matrix with diagonal elements equal to 100 and off-diagonal elements equal to 10. These are diffuse priors implying little prior information on the parameters. This is acceptable given the very large amount of data contributing to this analysis. Each model was fit using PROC MCMC in SAS Software, version 9.4.

In addition to establishing the age and DM effects for this sample, we estimated prediction intervals for a new subject at each age and in each DM group. These intervals were generated using the MCMC posterior simulations following methods in Gelman et al. (2014).

RESULTS

Table 2 displays the characteristics of the 222 participants that comprise our sample. As anticipated, this Veteran sample was mostly male (89%). Participants ranged in age from 26 – 71 years (mean age 51 yrs). Neither sex nor race/ethnicity varied substantially across the groups. PTA averaged between the left and right ear varied from less than 1 dB HL to over 32 dB HL, and averaged about 15 dB HL. A slightly smaller number of participants with type 2 DM were dependent on insulin to control blood glucose compared with those who were not. Those with IDDM had over twice the disease duration compared with those with NIDDM despite similar mean ages. Insulin use and disease duration could be thought of in the context of severity of disease meaning those dependent on insulin and with longer duration could be characterized as having greater severity of DM. Conceptually this is important when considering other disease-related effects such as diabetic retinopathy, neuropathy and nephropathy (Hansen & Bodkin 1986; Duckworth et al. 2011). Further, it is reported that individuals with DM have higher rates of macrovascular disease than those without (Duckworth et al. 2011), which can clearly be seen in our sample. Compared to control participants, those with DM also had higher rates of heart disease, high blood pressure and stroke. As expected, both short (blood glucose) and long-term (HbA1c) blood sugar level metrics were worse for those with DM compared to controls, and were higher for those with IDDM compared to those with NIDDM.

The grand mean waveform response is shown for each stimulus condition and participant group in Figure 2. The two traces in each panel further subdivide groups by the sample mean age. More specifically, a separate trace is shown for participants <50 years and ≥50 years. The number of participants < 50 years (solid lines in each panel) is as follows: No DM=43, NIDDM=31, IDDM=21. The number of participants ≥50 years (dashed lines in each panel) is as follows: No DM=71, NIDDM=30, IDDM=26. The most obvious effect is that P2 latencies seem longer for older compared with younger participants, but this could be related to hearing differences associated with age (Oates et al. 2002) in these unadjusted data. Although less pronounced than the apparent age effect on P2, the N1 and P2 latencies also seem somewhat prolonged among the older participants with NIDDM. Using the gross division of young versus old, the age differences appeared less pronounced for participants

with IDDM; if anything some trends were reversed. This analysis is convenient for representing some of the major features of the data, but obscures details of the sample.

Figure 3 displays scatter plots of all CAEP peak measures against age for binaural, left, and right ear stimulus presentation conditions. Participant group is denoted by symbol type and color with each control participant indicated by a black circle, NIDDM by a blue triangle and IDDM by a red circle. A loess smoothed curve is fit to the data to capture general patterns within participant groups. Latency is displayed in ms while N1-P2 amplitude is in μV as a function of continuous age. Across groups, N1 and P2 latencies (top two rows) show trends toward an increase with age, particularly P2 latency. In general, N1 and P2 latencies also seem somewhat prolonged (i.e. overall higher loess curves) among the participants with DM. N1 latency shows slightly accelerated aging after about 50 years, suggesting a possible non-linear effect of age. It may be the case that the linear model is not as appropriate for the N1 latency, due perhaps to the more limited data and greater scatter at the age margins of our sample. However, residual analysis did not show any gross deviations from the linear model. N1-P2 amplitude (bottom row) shows a weaker association with age though trends in some groups appear to decline with increasing age, also after about 50 years (control and NIDDM). Also note the consistent patterns in the data across columns, which suggest a high degree of correlation among responses to binaural, left, and right ear stimuli. This feature is exploited in the multivariate response regression model described in equation (1).

Figure 4 shows similarly structured scatter plots of CAEP against PTA. Using the clinical pure tone average (PTA) of 500, 1000 and 2000 Hz, we see much less convincing evidence of an effect of hearing loss accounting for changes in CAEPs (Figure 4). The loess curves are nearly flat across CAEP and ears.

Table 3 shows partial correlation coefficients between each CAEP peak and age and PTA for each DM group and stimulus presentation condition. Overall, we see a stronger linear relationship between age and CAEP than between PTA and CAEP, after partialling with respect to the other predictor. The strongest relationships are seen between P2 latency and age, particularly in the NIDDM group, which vary from $r=0.33$ to 0.37 . Somewhat weaker relationships are seen in the IDDM and non-diabetic groups for that response. The partial correlations in Table 3 are overall relatively small, reflecting the highly dispersed nature of CAEPs seen in Figures 3 and 4.

We fit the model described in the methods section and found little variation in the intercepts, age effects, or PTA effects across stimulus conditions. This means that the effects of age, PTA, and DM are effectively captured by the parameters μ_d , α_d , and β_d in equation (3). More specifically, the variance components for the ear stimulus-level effects $|\sigma|$ are an order of magnitude smaller than the variance components denoted by $|\tau|$ in equation (3). Accordingly, we can simplify the results of this analysis by focusing on the μ_d , α_d , and β_d instead of the ear-specific effects of age, PTA, and DM on each CAEP outcome. The full results of the Bayesian analysis with all estimated regression coefficients across all groups and stimulus conditions are given in Supplementary Appendix A. Supplementary Appendix B provides standard linear regression coefficients estimated by conventional methods.

The estimates of the DM-specific effects are shown in Table 4 (N1 latency), Table 5 (P2 latency), and Table 6 (N1-P2 amplitude). The columns labeled ‘Mean’, ‘LCL’, and ‘UCL’ are the posterior mean, lower, and upper 95% Bayesian confidence intervals for each effect. These intervals show the range of effect sizes within which we are nearly certain the true effect lies. Bayesian analysis does not have the conventional notion of “statistical significance”, though one is nearly certain that the effect in question is not zero if the Bayesian confidence interval does not include zero. Our best estimate of each effect is expressed by the posterior mean. As noted in the methods section, the intercept effects are the mean CAEP for a random participant aged 50 with 15 dB PTA. The age effects are the change in CAEP (ms or μV) per year of life, and the PTA effects are the change in CAEP (ms or μV) per dB of PTA. The Bayesian analysis also offers a straightforward method of contrasting groups. In particular, we can estimate the probability that each DM group has larger or smaller effects than the participants without DM. These are shown in the last two columns of each table.

Table 4 shows the posterior mean N1 latency intercept at about 108 ms for the no-DM group (95% confidence interval = 106 to 110 ms), about 111 ms for NIDDM (95% confidence interval = 108 to 113 ms), and about 110 ms for IDDM (95% confidence interval = 107 to 113 ms). We are 89% certain that the N1 latency intercept is bigger among participants with IDDM compared to non-diabetics, and 95% certain that the NIDDM intercept is bigger than controls. However, these probabilities are associated with only about a 2–3 ms longer N1 latency among participants with DM compared those without. Thus on average, individuals with DM likely have a relatively small, perhaps clinically irrelevant pre-attentive cortical processing delay. We are less certain about DM differences in effects of age and PTA on N1 latency. Compared with no-DM controls, the rate of change in N1 latency with age appears to be increased in NIDDM participants by about 0.36 ms per year of life (95% confidence interval = 0.0 to 0.72 ms), and whereas we are about 84% certain that this latency change with age is greater as compared with the no-DM group, this effect is not precisely estimated as indicated by the wide confidence interval. The N1 latency change with age may also be greater in IDDM participants; however, the probability of this is only 69%. As noted in Figure 4, there is also little evidence of an effect of PTA on N1 latency in this sample. All confidence intervals cover 0 ms per dB of PTA, and have a mean effect of a 1/10 ms change or less in latency per dB of PTA.

Results of the P2 latency analysis are shown in Table 5. DM participants have convincingly higher P2 latency compared to non-diabetics. We are 98% certain that NIDDM participants have longer P2 latencies than no-DM controls, and 93% certain of this for IDDM participants. The effect size for these differences is similar (7 or 9 ms) whether or not insulin is required to manage the disease (191 ms – 184 ms = 7 ms for the IDDM group; 193 ms – 184 ms = 9 ms for the NIDDM group). Age effects are almost certainly greater than zero in the no-DM and NIDDM groups. The size of the age effect is also fairly consistent across these two groups at 0.88 and 1.08 ms increase in P2 latency per year of life, or 9–11 ms increase per decade. The observed increase in P2 latency with age is slightly less for the IDDM group, although it is also imprecisely estimated as indicated by the large confidence interval. Overall, there is little evidence to suggest that DM influences the rate of change with age of the P2 peak. As with N1 latency, there is little evidence of an effect of PTA on

P2 latency. These effects are small (less than 0.3 ms per dB PTA) and imprecisely estimated with wide confidence intervals covering zero.

Table 6 summarizes results for N1-P2 amplitude. As was noted in Figures 3 and 4, there is little evidence to support any aging or PTA effects on N1-P2 amplitude. However, non-diabetic participants appear to have slightly larger N1-P2 amplitude, amounting to about .1 to .3 μV larger than NIDDM and IDDM, respectively. We are only 68% certain that NIDDM is associated with smaller N1-P2 amplitude than no-DM controls and 78% certain that IDDM is associated with smaller N1-P2 amplitude than controls, which is not as convincing as some of the intercept effects observed in Tables 3 and 4.

To summarize:

1. There is little variation across presentation conditions (left, right, and binaural) on any CAEP peaks in any of the groups.
2. There is considerable evidence of longer N1 latency and longer P2 latency among DM participants than among controls. These effects amount to a small (2–3 ms longer) average N1 latency difference and a larger (7–9 ms longer) average P2 latency difference for IDDM and NIDDM participants compared with no-DM controls.
3. There is some evidence for accelerated aging in the N1 latency among NIDDM.
4. P2 latency appears to increase by about 9 ms per decade among controls, and there is little support for aging effects on the N1-P2 amplitude.
5. There is also little support for a PTA effect on any CAEP peak in this sample.

Figure 5 presents all of the age models for each outcome (rows) and each DM group (columns) from the estimates shown in Tables 4–6. All the observed responses are also shown on these plots. The thick lines and shaded regions show the fitted mean CAEP response and 95% Bayesian confidence intervals for the sample means from the multi-level model of the data set with PTA held constant at 15 dB HL. The thin lines show 95% Bayesian prediction intervals for a new response, that is, the interval in which we expect to see a response from any new individual that could be sampled. The last column of Figure 5 shows all of the fitted models overlaid for comparison. This figure shows the differential rate of aging in the N1 Latency response among participants with DM and overall higher P2 Latency among participants with DM. The N1-P2 amplitude is flat across participant groups. The abundance of data allows us to estimate the mean response relatively precisely, resulting in narrow confidence intervals for the mean CAEP response across the ages where the bulk of the data lay. Thus the age and DM effects are precisely estimated at a group level for much of our sample, with less precise estimates at the edges of the age range. However, CAEP peaks tend to be quite variable, so a wide range of N1 and P2 latencies or N1-P2 amplitude is predicted in any other sample. Moreover, we cannot use the model to precisely predict what response would be obtained for any individual tested.

DISCUSSION

Accumulating evidence suggests that DM degrades various aspects of auditory function, which would not be surprising given the microvascular and central nervous system changes associated with the disease. As part of a study of DM-related changes in auditory function among the VA Primary Care population, this paper reports results for CAEPs. Here we characterize the influence of type 2 DM and insulin dependence on the age-related trajectory of N1 P2 peaks. Participants were previously shown to exhibit both age- and DM-group related hearing differences (Austin et al. 2009). Therefore it was considered important that we statistically adjust for any residual hearing effects in order to more accurately determine how central auditory changes with age differ with DM.

The most convincing results of this analysis are that N1 and P2 latencies are prolonged among participants with DM compared to those without (on average by 2–3 and 7–9 ms, respectively), and that P2 latency increases among individuals without DM by about 9 ms per decade. Thus the P2 peak changes associated with DM, though small in absolute terms, seem relatively important when compared with normal age effects. These latency results, which represent information about the timing of sound stimulus encoding at the cortex, indicate that pre-attentive neural conduction is slower among older compared with younger individuals, and even slower still among patients with DM. Smaller and somewhat less convincing effects were found in accelerated aging for N1 latency and slightly smaller N1-P2 amplitude among DM participants.

For P2 latencies our results support a model of DM-related changes such as shown by the solid gray line in Figure 1. Normal auditory senescence occurs across the population, but, on average, the onset of DM may induce a rapid deterioration of CAEPs. Diagnosis and some degree of treatment returns the deterioration of CAEPs to the normal rates of decline with age observed among individuals without DM, but only after some amount of damage has been done. Whereas our results estimate the trajectory of P2 latency by age for the average participant in each group, such a model of DM changes may be reasonable at the individual level. Consistent with this model, early detection and treatment of DM is known to decrease the risk of developing some of the commonly described DM microvascular complications, including retinopathy, neuropathy and nephropathy (ADA, 2015). However, treatment for DM may not occur until complications have begun to develop because many early symptoms of the disease (e.g., elevated blood glucose, blood pressure and cholesterol levels) can go undetected (Phillips et al. 2001).

Finally, we found no evidence to support the view that responses among IDDM participants were more impacted than NIDDM, although their responses tended to be more variable. Based on the higher number of health complications, poorer HbA1c and longer disease duration for IDDM versus NIDDM participants, we have historically considered IDDM to be the more severe subgroup of DM; however, it is possible that insulin provides some relative protective effect on cortical responses unrelated to its effect on blood sugar or on other DM complications.

Comparison with results of prior studies

There are scant data in the literature describing the impact of DM on CAEPs with which to compare present results. Manjarrez et al. (2007) found substantial effects of DM on CAEP amplitudes and latencies when comparing groups of normal hearing females with and without DM2 on responses elicited using a 1.5 Hz click delivered binaurally at 70, 90 and 103 dB SPL using an interstimulus interval (ISI) of about 1000 ms. Mean latencies of N1 and P2 increased with stimulus level for both groups; however, statistically significant latency differences were present at each level tested. At a level of 70 dB SPL, mean latency differences between groups were 22 ms for N1 and 34 ms for P2. The differences increased slightly to 28 ms for N1 and 49 ms for P2 at a level of 103 dB SPL. The diabetic females also exhibited higher amplitudes, particularly at higher stimulus levels, compared with controls though only the amplitude/level slopes were evaluated for statistical significance. Slopes were significantly increased (steeper) in the diabetic participants. In contrast, the present study yielded little evidence of DM effects on amplitudes, and comparatively smaller DM-related N1 and P2 peak delays in a slightly older, predominantly male sample of Veterans. Sampling differences likely explain some of the differences between studies. Additionally, unlike the present report, Manjarrez and colleagues did not account for age differences when estimating DM effect sizes, even though the diabetic females were on average 5 years older than controls. They also did not report hearing data for either group, thus it is unclear whether or not DM-related hearing differences existed which could have contributed to the CAEP differences observed between groups.

Several studies have investigated the effect of age on CAEP's using a homogenous paradigm, but in non-diabetics and with mixed results. Papanicolaou et al. (1984) recorded CAEPs to pairs of 1000 Hz tone bursts presented binaurally at 75 dB SPL in 9 young (22–33 years old, mean 27.4) and 8 older participants (67–84 years old, mean 75.8). The silent interval separating the bursts was fixed at 350 ms; however, the rate of presentation of the stimulus pair was varied to yield ISIs of 650, 1650 and 4650 ms. The N1-P2 amplitudes were greater in the younger participants for the slower stimulation rates only. Additionally, at slow rates, amplitude differences between the two tones in the pair emerged for the young, but less so for older participants. The only significant age-related latency effect was an increase in P2 latency in the older participants. For the first tone, P2 was delayed 12.9 ms, 34.4 ms, and 16 ms at 650, 1650 and 4650 ms, respectively. Using a 1 sec ISI, we found largely compatible results showing no effect of age on the N1 peak and somewhat larger age-associated P2 latency shifts. In a study of 30 individuals (14 male; 16 female) age 20–80 years, Laffont et al. (1989) found no significant age related effects on the N1 or P2 latencies nor any age effect on amplitude/level slopes using 1000 Hz tone burst stimuli presented binaurally. However, they used a short ISI of 0.5 seconds, which could have precluded the ability to detect age effects according to Papanicolaou et al. (1984).

More recently, Kim et al. (2012) investigated N1 and P2 in relation to both stimulus level and signal to noise ratio (SNR) in groups of 8 young (24–20 year olds, mean 26.5) and 8 older (60–76 year olds, mean 65.8) normal hearing participants. The 1000 kHz tones were presented to the right ear of each participant using an ISI of 1.43 sec at levels ranging from 60 to 100 dB SPL, in quiet and in the presence of a 70 dB SPL background noise. Using

only their data for the quiet condition for comparison, they found longer (by ~19.3 ms) N1 latencies in older adults at 60 dB SPL only and no significant age effects for P2 latencies. There were no significant age effects for N1-P2 amplitudes. For CAEPs obtained in noise, N1 latencies were prolonged only at 70 dB SPL (the 0 SNR condition). Although not statistically significant, the P2 latencies were also prolonged in older compared with younger adults with the largest effect (about 28 ms) noted at the 70 dB SPL (SNR=0) presentation level. Because the age effects were present only for the most challenging listening conditions, these investigators concluded that the findings were the result of poor neural synchrony in the older participants, which should be most pronounced at low levels or in noise.

Finally, Lijffijt et al. (2009) compared the effects of age, sex, education and intelligence on CAEPs elicited using 1000 Hz paired-clicks delivered at 80 dB SPL with an ISI of 500 msec between the first and second click (S1 and S2) and a randomized interval of 8–10 sec between presentations of the pairs. Stimuli were delivered binaurally to the 60 subjects (26 males and 34 females) aged 18–54 years with good hearing by self-report. Focusing on P2 responses to S1, only amplitude was found to be significantly correlated with age.

A number of studies have examined CAEP changes with age using tonal stimuli presented in an oddball paradigm (i.e., frequency and infrequent stimuli are presented within the same stimulus block) to elicit N1 and P2 peaks. Most reveal limited age-related delays in P2 latency with effect sizes ranging from 2.3 ms per decade to 7 ms per decade (Goodin et al. 1978; Iragui et al. 1993; Pekkonen et al. 1995; Picton et al. 1984; Kerr et al. 2010). Significant age-related delays in N1 latency are less often present (Goodin et al. 1978; Iragui et al. 1993; Pekkonen et al. 1995). Still other oddball paradigm studies find no significant age effects on N1 or P2 peak latencies (Woods 1992; Polich 1997).

The present estimates of age-related CAEP changes were obtained in a sample that was larger by a factor of 10 compared with most previously published studies. In spite of the variability inherent in CAEP metrics (as shown in Figures 3 and 4 of the present report) and differences in study methodology and samples, our age-related CAEP changes, which were greater for P2 compared with N1 after adjusting for any influence of PTA, are compatible with several previous reports (Papanicolaou et al. 1984; Pekkonen et al. 1995; Picton et al. 1984; Kerr et al. 2010).

Other measures in this cohort

DM-related effects for the Veterans who contributed data to the present report have also been described for responses that reflect auditory system function at the periphery (pure tone threshold) and within the brainstem (ABR) (Austin et al. 2009; Konrad-Martin et al. 2010). Significant effects of DM on ABR were found only for IDDM participants in the youngest age group (those < 50 years old) in whom ABR wave V amplitude and latency and the I–V latency interval were significantly correlated with HbA1c and self-reported poor circulation in the feet and/or hands. Thus in contrast to the present results for CAEPs, the ABR abnormalities were greater among those with more severe disease. Pure-tone threshold elevations associated with DM were also age-dependent with significant NIDDM differences from controls found only in the youngest group (Austin et al. 2009). For the two older age

groups, threshold differences were observed only for those with IDDM. These results suggest that at older ages, normal senescence may have obscured the association between mild DM and pure tone thresholds and between even more severe DM and ABRs. The current analysis reveals DM effects on CAEPs at any given age (represented in the sample) for P2 latency. Compared with the DM effects on P2, the age effect is much smaller. This finding warrants further investigation of DM-related changes in cortical function and indicates that pre-attentive cortical function should be considered when interpreting effects of DM on electrophysiological measures of attention and memory.

Age-related effects on ABR have also been described for the no-DM controls who contributed data to the present study in Veterans. Results of the present study indicate that among controls, the N1-P2 amplitude shows no systematic age-related change. In contrast, all three primary ABR peak amplitudes decrease substantially with age among Veterans, with greater percent change observed for wave III (43%) vs. wave V (34%) (e.g., Konrad-Martin et al. 2012). Thus the lack of an age effect on N1-P2 amplitude may be an indication of compensatory changes in the brain that may serve to keep the overall gain of the system constant (Schaette & McAlpine 2011). In this cohort, aging in the absence of DM is associated with increased latencies of electrophysiological measures arising from the auditory nerve (ABR wave I) (Konrad-Martin et al. 2012) and auditory cortex (P2 latency) separate from any age-related changes in hearing.

Clinical Implications

The major DM effect is with P2 latency, suggesting DM is associated with slowed pre-attentive neural conduction. The effect may be clinically significant *for the average individual* with DM given that it is large compared to the age effect on P2, however, our results also suggest it is not possible to accurately predict the magnitude of the DM effect for a specific patient.

Given the findings in this study and elsewhere that central auditory system deficits affect individuals with DM, and these individuals are also at a higher risk for hearing impairment, they may have complex auditory rehabilitative needs similar to those of many elderly individuals without DM. Considerations for the aural rehabilitation of patients presenting with both peripheral and central auditory dysfunction are beyond the scope of this report, but can be found elsewhere (e.g., Saunders et al. 2014).

Lack of evidence for more rapid aging of P2 among patients with DM suggests an effect that presents early in the disease process. The present results therefore underscore the need for community-based screenings to identify early symptoms of DM so that affected individuals can be identified and provided appropriate treatment as soon as possible.

Limitations

It is important to distinguish between aging and age differences. Aging is a longitudinal process that is most precisely estimated by following large groups of participants, with and without DM, over a long period of time. Age differences, such as those shown in this analysis, are the differences in CAEP among people who differ in age. Aging and age differences are equivalent if there are no cohort effects, which is often very difficult to

accurately ascertain. Thus the results of this study would benefit from confirmation from a longitudinal study.

Another limitation of this study is that it examined responses from a small number of electrode sites; more electrode sites may help to further disambiguate DM from age effects. However, the fact that we found effects of DM suggests that a more complete study with a larger electrode array would be fruitful.

Our data were obtained in Veterans receiving health care at the VA. Thus the majority of individuals were male and we were unable to evaluate the influence of sex on DM and age effects. We modeled the correlation among left, right, and both ear responses. This is one way to adjust the reported effect sizes with respect to overall larger or smaller amplitudes and longer or shorter latencies across individual participants as might be related to sex or head size. Another approach would have been to adjust for sex and/or include a participant-specific intercept in our multiple regression approach. The approach we used was more computationally efficient and therefore we considered it to be a more parsimonious method. Finally, by virtue of their military service, our participants could have greater noise exposure in their histories compared with a different sample. However, subjects were selected for having no severe hearing deficiencies, which could lessen any impact of this.

Because nearly 85% of those contacted to participate declined or were excluded upon examination, the remaining 15% of eligible participants meeting study criteria can be viewed as a convenience sample. This is true of most studies that have examined effects of age and DM on CAEPs; however, the present sample is an order of magnitude larger than most previously published studies improving the generalizability of results.

CONCLUSION

Normal age changes in CAEPs include a P2 latency increase of 9 ms per decade of life. DM-related effects include a small (2–3 ms longer) average N1 latency and a larger (7–9 ms longer) average P2 latency for IDDM and NIDDM participants compared with no-DM controls. Thus pre-attentive cortical processing is impacted by DM, and the effect is similar whether or not insulin is required to manage the disease. Our results also suggest that whereas N1 latency changes with age are more pronounced among individuals with versus without DM, we were unable to uncover evidence for more rapid aging of P2 among patients with DM. The damage responsible for the major DM-related differences may therefore be occurring early in the DM disease process. These results should be verified using a longitudinal study design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
 Theoretical models of possible effects of senescence and diabetes mellitus (DM).

Figure 2. Grand average CAEP waveforms can reveal major features of the data, but obscure important details of the sample

Grand average waveforms are shown for participants <50 years (dashed line) and ≥ 50 years (solid lines). Data are presented separately for binaural, left ear, and right ear presentation conditions (columns) and participant group (rows). The number of participants < 50 years is as follows: No DM=43, NIDDM=31, IDDM=21. The number of participants ≥ 50 years is as follows: No DM=71, NIDDM=30, IDDM=26.

Figure 3. Raw data trend toward an increase in CAEP latencies with age and DM

Observed CAEP peak measures are plotted by age. Each CAEP metric is given in a separate row with presentation condition (binaural, left, and right ear) indicated by column.

Participant group is denoted by symbol type and color as indicated in the figure. A loess smoothed curve is fit to the data for each participant group.

Figure 4. Raw CAEP data do not show a consistent trend with PTA

Observed CAEP peak measures are plotted here by PTA. Format is the same as for Fig. 4.

Figure 5. Summary of model results showing statistically adjusted, age trajectories for each DM group and the associated confidence interval

Model results overlay the observed data; the thick solid lines are the fitted mean response and open circles are the observed data. The shaded region is a 95% Bayesian confidence interval for the fitted mean, corresponding to the region within which we are 95% certain the true mean lies. The thin, solid lines show the 95% prediction intervals, corresponding to the region in which we expect a new CAEP measurement to lie. Note that confidence intervals

are wider at the extremes of the age range where data are less plentiful, particularly for participants with DM.

Table 1

Number of participants per cortical evoked potential (CAEP) measure by presentation condition and participant group^I.

		<i>Binaural</i>	<i>Left</i>	<i>Right</i>
<i>CAEP Metric</i>	<i>Group</i>			
<i>N1 Latency</i>	<i>No DM</i>	112	111	111
	<i>NIDDM</i>	58	57	57
	<i>IDDM</i>	44	47	44
<i>P2 Latency</i>	<i>No DM</i>	111	111	110
	<i>NIDDM</i>	61	60	61
	<i>IDDM</i>	47	45	47
<i>N1-P2 Amplitude</i>	<i>No DM</i>	111	111	110
	<i>NIDDM</i>	61	60	61
	<i>IDDM</i>	47	45	47

^INo diabetes (No DM); not insulin dependent (NIDDM); insulin dependent (IDDM).

Table 2

Participant characteristics.

		No DM			NIDDM			IDDM			All		
N		114			62			47			223		
<i>Age (years)</i>		<i>Mean</i>			52.0			49.9			50.1		
		<i>Min</i>			26.0			30.0			36.0		
		<i>Max</i>			71.0			66.0			63.0		
<i>Sex</i>													
<i>Female</i>		<i>N</i>			17			4			4		
		<i>%</i>			14.9			6.5			8.5		
<i>Male</i>		<i>N</i>			97			58			43		
		<i>%</i>			85.1			93.5			91.5		
<i>Ethnicity</i>													
<i>American Indian/Alaskan Native</i>		<i>N</i>			3			.			1		
		<i>%</i>			2.6			.			2.1		
<i>Asian or Pacific Islander</i>		<i>N</i>			2			.			.		
		<i>%</i>			1.8			.			.		
<i>Black</i>		<i>N</i>			7			3			4		
		<i>%</i>			6.1			4.8			8.5		
<i>Hispanic</i>		<i>N</i>			6			.			1		
		<i>%</i>			5.3			.			2.1		
<i>No answer</i>		<i>N</i>			12			4			4		
		<i>%</i>			10.5			6.5			8.5		
<i>Other</i>		<i>N</i>			2			1			1		
		<i>%</i>			1.8			1.6			2.1		
<i>White</i>		<i>N</i>			82			54			36		
		<i>%</i>			71.9			87.1			76.6		
<i>Left/Right ear mean PTA 500, 1000 and 2000 Hz</i>		<i>Mean</i>			13.6			16.6			17.0		
		<i>Min</i>			0.8			5.0			5.8		
		<i>Max</i>			32.5			32.5			30.8		
<i>Disease Duration (years)</i>		<i>Mean</i>			0.0			5.1			11.5		

	No DM			NIDDM	IDDM	All
N	114			62	47	223
	<i>Std</i>			3.8	6.8	6.2
<i>Heart Disease</i>						
<i>No</i>	<i>N</i>	106		54	35	195
	<i>%</i>	93.0		87.1	74.5	87.4
<i>Yes</i>	<i>N</i>	8		8	12	28
	<i>%</i>	7.0		12.9	25.5	12.6
<i>High BP</i>						
<i>No</i>	<i>N</i>	69		19	16	104
	<i>%</i>	60.5		30.6	34.0	46.6
<i>Yes</i>	<i>N</i>	45		43	31	119
	<i>%</i>	39.5		69.4	66.0	53.4
<i>Stroke</i>						
<i>No</i>	<i>N</i>	110		59	44	213
	<i>%</i>	96.5		95.2	93.6	95.5
<i>Yes</i>	<i>N</i>	4		3	3	10
	<i>%</i>	3.5		4.8	6.4	4.5
<i>Blood Glucose (mg/dl)</i>	<i>Mean</i>	107.6		179.9	230.8	153.7
	<i>Std</i>	19.0		96.2	119.5	90.7
<i>HbA1c (%)</i>	<i>Mean</i>	5.3		7.3	8.0	6.4
	<i>Std</i>	0.5		1.9	2.2	1.9

Table 3

Partial correlation coefficients between CAEP metrics and either age or PTA by participant group and presentation condition.

<i>CAEP Metric</i>	<i>Presentation Condition</i>	<i>No DM</i>		<i>NIDDM</i>		<i>IDDM</i>	
		<i>Age</i>	<i>PTA</i>	<i>Age</i>	<i>PTA</i>	<i>Age</i>	<i>PTA</i>
<i>N1 Latency</i>	<i>Binaural</i>	0.11	-0.04	0.25	-0.13	0.17	0.06
	<i>Left</i>	0.20	0.09	0.28	-0.12	0.05	-0.02
	<i>Right</i>	0.16	0.05	0.27	-0.08	0.11	0.06
<i>P2 Latency</i>	<i>Binaural</i>	0.31	0.08	0.34	0.02	0.10	0.01
	<i>Left</i>	0.20	0.10	0.33	-0.11	0.09	-0.05
	<i>Right</i>	0.31	-0.02	0.37	0.05	0.27	0.02
<i>N1-P2 Amplitude</i>	<i>Binaural</i>	-0.04	0.05	-0.06	-0.00	-0.20	-0.05
	<i>Left</i>	-0.11	0.06	-0.13	-0.00	0.09	-0.09
	<i>Right</i>	-0.08	-0.02	-0.05	0.01	0.12	-0.09

Table 4

The N1 latency multivariate response regression model estimates¹ for age and PTA effects. In addition, the probability² is given that the mean N1 latency in participants with DM is greater or less than the mean N1 latency in participants without DM.

Effect Size ³	Group	Posterior Mean		Probability DM group greater than No DM group		Probability DM group less than No-DM group	
		LCL	UCL				
Intercept: Mean response at age = 50 years and PTA=15 dB	No DM	108.06	105.85	110.27	.	.	.
	NIDDM	110.76	108.32	113.21	95%	5%	5%
	IDDM	109.94	107.11	112.76	89%	11%	11%
Age Effect: Change in N1 Latency (ms) per year of life	No DM	0.15	-0.11	0.41	.	.	.
	NIDDM	0.36	-0.00	0.72	84%	16%	16%
	IDDM	0.29	-0.20	0.79	69%	31%	31%
PTA Effect: Change in N1 Latency (ms) per dB of PTA	No DM	0.01	-0.17	0.19	.	.	.
	NIDDM	-0.05	-0.29	0.19	39%	61%	61%
	IDDM	-0.02	-0.25	0.22	46%	54%	54%

¹The 'Mean', 'LCL', and 'UCL' are the posterior mean, and lower or upper 95% Bayesian confidence intervals for each effect.

²Percentages may not total 100 due to rounding error.

³Age effect size is with PTA=15 dB HL; PTA effect size is with age=50 years.

Table 5

The P2 latency multivariate response regression model estimates¹ for age and PTA effects. In addition, the probability² is given that the mean N1 latency in participants with DM is greater or less than the mean N1 latency in participants without DM.

Effect Size ³	Group	Posterior Mean	LCL	UCL	Probability DM group greater than No DM group	Probability DM group less than No-DM group
<i>Intercept: Mean response at age = 50 years and PTA=15 dB</i>						
	No DM	183.92	179.60	188.25	.	.
	NIDDM	192.58	186.03	199.13	98%	2%
	IDDM	191.21	183.87	198.55	93%	7%
<i>Age Effect: Change in P2 Latency (ms) per year of life</i>						
	No DM	0.88	0.26	1.49	.	.
	NIDDM	1.08	0.27	1.89	66%	34%
	IDDM	0.65	-0.34	1.65	35%	65%
<i>PTA Effect: Change in P2 Latency (ms) per dB of PTA</i>						
	No DM	0.03	-0.38	0.44	.	.
	NIDDM	0.10	-0.38	0.58	56%	44%
	IDDM	-0.02	-0.46	0.43	44%	57%

¹The 'Mean', 'LCL', and 'UCL' are the posterior mean, and lower or 95% Bayesian confidence intervals for each effect.

²Percentages may not total 100 due to rounding error.

³Age effect size is with PTA=15 dB HL; PTA effect size is with age=50 years.

Table 6

The N1-P2 amplitude multivariate response regression model estimates¹ for age and PTA effects. In addition, the probability² is given that the mean N1 latency in participants with DM is greater or less than the mean N1 latency in participants without DM.

Effect Size ³	Group	Posterior Mean		Probability DM group greater than No DM group		Probability DM group less than No-DM group	
		LCL	UCL				
Intercept: Mean response at age = 50 years and PTA=15 dB	No DM	5.23	4.80	5.66	.	.	.
	NIDDM	5.11	4.66	5.56	34%	66%	
	IDDM	4.99	4.55	5.43	22%	78%	
Age Effect: Change in N1-P2 amplitude (μV) per year of life	No DM	-0.00	-0.04	0.04	.	.	.
	NIDDM	-0.01	-0.06	0.04	46%	54%	
	IDDM	-0.00	-0.07	0.06	52%	49%	
PTA Effect: Change in N1-P2 amplitude (μV) per dB of PTA	No DM	-0.00	-0.05	0.04	.	.	.
	NIDDM	0.01	-0.04	0.06	62%	38%	
	IDDM	-0.01	-0.05	0.04	46%	54%	

¹The 'Mean', 'LCL', and 'UCL' are the posterior mean, and lower or upper 95% Bayesian confidence intervals for each effect.

²Percentages may not total 100 due to rounding error.

³Age effect size is with PTA=15 dB HL; PTA effect size is with age=50 years.