An Epidemiologic Study of the Association between Free Recall Dichotic Digits Test Performance and Vascular Health

Mary E Fischer[1], **Karen J Cruickshanks**[1,2], **Lauren K Dillard**[3], **David M Nondahl**[1], **Barbara E K Klein**[1], **Ronald Klein**[1], **James S Pankow**[4], **Ted S Tweed**[1], **Carla R Schubert**[1], **Dayna S Dalton**[1], and **Adam J Paulsen**[1]

[1]Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI

[2]Department of Population Health Sciences, University of Wisconsin, Madison, WI

[3]Department of Communication Sciences and Disorders, University of Wisconsin, Madison, WI

[4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN

Abstract

BACKGROUND—Associations between vascular health-related factors and hearing loss defined using audiometric pure-tone thresholds have been found. Studies have not focused on a potential relationship between vascular health-related factors and central auditory processing.

PURPOSE—The purpose of this study was to evaluate, on a population level, the relationship of vascular health-related factors with central auditory function.

RESEARCH DESIGN—Cross-sectional, population study

STUDY SAMPLE—Subjects were participants in the Epidemiology of Hearing Loss Study (EHLS) or the Beaver Dam Offspring Study (BOSS), prospective studies of aging and sensory loss. BOSS participants were the adult offspring of participants in the EHLS. Participants who completed the Dichotic Digits Test (DDT) during the fourth examination period of EHLS (2008–2010) or the second examination period of BOSS (2010–2013) were included (n=3655, mean age = 61.1 years).

DATA COLLECTION AND ANALYSIS—The DDT-free recall test was conducted using 25 sets of triple digit pairs at a 70 dB HL presentation level. The total number of correctly repeated digits from the right and left ears was converted to a percentage correct and used as an outcome. The percentage correct in the left ear was subtracted from the percentage correct in the right ear and used as an outcome. Vascular health-related measures obtained during the examination included blood pressure, mean carotid intima-media thickness, femoral pulse wave velocity (PWV), hemoglobin A1C, non-HDL cholesterol, and in the EHLS participants, C-reactive protein and interleukin-6. Information on vascular health-related history and behaviors was self-reported. General linear modeling produced estimates of the age-sex adjusted least squares means for each

Corresponding author: Mary E. Fischer, PhD, Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin-Madison, 610 Walnut Street, 10th Floor WARF, Madison, WI, 53726-2336 USA. fischer@episense.wisc.edu; Telephone: 608-265-8845; FAX: 608-265-2148.

vascular factor and multiple linear regression was used for multivariable modeling of each outcome.

RESULTS—After multivariable adjustment, participants with diabetes had a significantly lower (worse) mean DDT-free recall total score (−2.08 percentage points, p < 0.001) than those without diabetes. Participants who exercised at least once per week had a significantly higher (better) mean DDT-free recall total score (+1.07 percentage points, p < 0.01) than participants who did not exercise at least once per week. Alcohol consumption was associated with a higher DDT-free recall total score (+0.15 percentage points per +25 grams ethanol, p < 0.01). In multivariable modeling of the right-left ear difference in DDT-free recall scores, participants with a history of cardiovascular disease (CVD) or higher PWV demonstrated significantly larger differences (CVD: +3.11 percentage points, p = 0.02; PWV: + 0.36 percentage points per 1 m/s, p < 0.01). Higher levels of non-HDL cholesterol were associated with smaller right-left ear differences (−0.22 percentage points per 10 mg/dL, p = 0.01). Adjustment for handedness did not affect the results.

CONCLUSIONS—Vascular health-related factors may play a role in central auditory function.

Keywords

Dichotic listening tests; central auditory function; vascular health-related factors; epidemiology

INTRODUCTION

Central auditory processing dysfunction has been found to be related to cognitive dysfunction including decline, impairment, and dementia (Hällgren et al, 2001; Gates et al, 2002, 2008, 2010, 2011; Idrizbegovic et al, 2013; Fischer et al, 2017). The Dichotic Digits Test (DDT) is one of many measures used to evaluate central auditory processing (Musiek et al, 1991; Gates et al, 2008, 2010, 2011). In the DDT, single-syllable numbers, typically in double-digit or triple-digit pairs, are presented in both ears concurrently and in the free recall version of the test, individuals are asked to repeat all numbers. One reason that the DDT, as well as other dichotic speech recognition tests, are particularly cognitively challenging may be because the competing signals result in the suppression of the ipsilateral processing pathways and consequently in more reliance on the contralateral pathways (Hugdahl, 1995).

Older age is strongly related to poor performance on central auditory processing tests (Jerger et al, 1994; Wilson and Jaffe, 1996; Strouse et al, 2000; Hällgren et al, 2001; Gates et al, 2002, 2011; Roup et al, 2006; Fischer et al, 2017) and to a greater right ear advantage (REA) in recall of the presented material (Wilson and Jaffe, 1996; Strouse and Wilson, 1999a; Roup et al, 2006; Hommet et al, 2010; Fischer et al, 2017). A recent population study reported that females and those with a college degree performed significantly better on the DDT-free recall (Fischer et al, 2017). The Blue Mountains Hearing Study also found better performance by females on dichotic listening tests (Golding et al, 2006) but few additional factors have been studied or reported to be related to dichotic testing on a population level.

With respect to the relationship between vascular health-related factors and central auditory processing, a cross-sectional study in the Framingham cohort reported that a history of heart attack or stroke in females, and current smoking in men was related to performance on the

Synthetic Sentence Identification test, a test with competing message (Gates et al, 1993), and in a recent case-control study of stroke patients, cases had significantly higher rates of central auditory processing deficits than controls (Koohi 2017). It has also been reported that individuals with type 2 diabetes had higher speech thresholds in the Hearing in Noise Test (Frisina 2006). Associations between vascular health-related factors and pure-tone threshold hearing loss, have been found as well (Gates et al 1993; Cruickshanks et al, 1998a; Bainbridge et al, 2008; Kiely et al, 2012; Cruickshanks et al, 2015; Fischer et al, 2015). Factors found to be associated with the risk of hearing impairment in previous prospective studies include current smoking, waist circumference, and glycosylated hemoglobin (Cruickshanks et al, 2015), and subclinical atherosclerosis, as measured by carotid intima-media thickness and plaque, and body mass index (Fischer et al, 2015). Baseline hypertension has been reported to be related to hearing decline over an 11 year follow-up (Kiely et al, 2012) and findings from cross-sectional investigations have suggested associations between hearing loss and smoking (Cruickshanks et al, 1998a), coronary heart disease (Gates et al, 1993), and diabetes (Bainbridge et al, 2008). Physical exercise has been found to be inversely related to self-reported hearing problems (Curhan et al, 2013).

The purpose of the current study was to evaluate, on a population level, the relationship of vascular health-related factors with central auditory function. The total score on the DDT-free recall test was used as the measure of central auditory processing and vascular health-related history, measurements, and behavioral factors were considered as potential related factors. The relationship between these same factors and the right-left ear difference on the DDT-free recall test was also evaluated. The results may be useful in planning future prospective investigations of the predictors of central auditory decline or dysfunction.

METHODS

Study Population

Participants were part of the Epidemiology of Hearing Loss Study (EHLS) or the Beaver Dam Offspring Study (BOSS), prospective longitudinal studies of aging and sensory disorders. Participants from the baseline Beaver Dam Eye Study (BDES) (1987–1988) were eligible to participate in the EHLS and there were 3753 participants with an age range of 48 to 92 years in the EHLS baseline examination (1993–1995). Follow-up examinations occurred at 5 year intervals with >80% response rates. The data in the present study are from the fourth examination period of EHLS (2008–2010). Audiometric testing was administered to 1549 participants, out of which 1391 completed free recall and right ear-directed dichotic digits testing (Fischer et al, 2017). Reasons for not completing dichotic digits testing include hearing loss severity or asymmetry (n=103), not successfully completing the dichotic digits training exercise (n=13), requesting to stop (n=14), or other/unknown reasons (n=28). Details of the EHLS may be found in previous reports (Klein et al, 1991; Cruickshanks et al, 1998b, 2003b, 2010).

The adult offspring of the EHLS participants were eligible for the BOSS. At the time of the BOSS baseline examination (2005–2008), there were 3296 participants with an age range of 21 to 84 years. During the five-year follow-up examination (2010–2013), audiometric data were obtained from 2346 participants and dichotic digits testing data from 2264 participants.

The reasons for not completing dichotic digits testing were ineligibility due to hearing loss severity or asymmetry (n=28), not successfully completing the training (n=11), requesting to stop (n=26) or other/unknown reasons (n=17). Further details of the BOSS are found in previous reports (Zhan et al, 2010; Nash et al, 2011; Fischer et al, 2013, 2015).

There was a total of 3655 subjects (1600 males and 2055 females) included in the study with an average age of 61.1 years. Close to 4% of the study population were less than 40 years of age, 42% were 40 to 59 years, 45% were 60 to 79 years, and 9% were 80 years of age or older.

Approval for this research was obtained from the Health Sciences Institutional Review Board of the University of Wisconsin and informed consent was obtained from all participants prior to each examination.

Measurements

Participants underwent a series of standardized examinations and interviews, which were conducted by examiners who were trained and certified in all study protocols. Similar methods were used in the EHLS and BOSS.

Audiometric Testing

Audiometric testing was performed and hearing-related medical history questionnaires were administered. Testing was performed in accordance with American Speech-Language-Hearing Association guidelines in compliance with the American National Standards Institute standards (American Speech-Language-Hearing Association, 1978; American National Standards Institute, 1999; American National Standards Institute, 2010). Otoscopy and tympanometry were performed prior to pure tone audiometry. Testing was done in sound-treated booths using clinical audiometers (calibrated every 6 months), TDH-50P earphones and ER3-A inserts in cases of probable ear canal collapse. There were 49 participants tested using insert earphones in other locations. Pure tone air-conduction thresholds were obtained in both ears at 0.5, 1, 2, 3, 4, 6, and 8 kHz, and bone-conduction thresholds were obtained at 0.5, 2, and 4 kHz. Masking was used as necessary (Cruickshanks et al, 1998b, 2003). A four-frequency pure-tone average (PTA) at 0.5, 1, 2 and 4 kHz was calculated for each ear and used to categorize hearing loss severity of either ear (worse ear) as follows: No loss=PTA 25 dB HL (n=2412, mean PTA = 12.8 dB HL); mild loss =25<PTA 40 dB HL (n=799, mean PTA = 32.1 dB HL); moderate or marked loss =PTA>40 dB HL (n=444, mean PTA = 49.3 dB HL). There were 3067 participants with symmetrical hearing loss severity (both ears were in the same severity group), 221 participants where the right ear loss was more severe than the left ear, and 367 participants where the left ear loss was more severe than the right ear.

Dichotic Digits Test

In order to complete the DDT, participants had to accurately complete a training/practice task, in which 3 examples of single-digit, double-digit, and triple-digit pairs were presented. If the participant was unable to repeat any of the numbers in the single-digit or double-digit pairs, or did not attempt to repeat any of the numbers in the triple-digit pairs, the participant

was not tested on the DDT. The free recall and right ear directed recall conditions each consisted of 25 sets of triple-digit pairs (3 digits presented to each ear simultaneously) using single-syllable numbers 1 through 10, excluding 7, presented at 70 dB HL. The CD for the test was provided by Dr. Richard Wilson. In the free recall task, which was administered first, the participant was asked to repeat as many of the 6 digits as possible. The numbers of correctly repeated digits from the right and left ears were added together and the sum was used as the score for the DDT-free recall. The possible range for the score was 0–150 (75 per ear). The number correct was converted into percentage correct for analysis purposes. The right-left ear difference was calculated by subtracting the left ear percentage correct from the right ear percentage correct.

Vascular Health-Related Factors

A history of cardiovascular disease was defined as self-report of a physician diagnosed stroke, angina, or myocardial infarction. Hypertension was defined as having received a diagnosis of hypertension with current medication use, or having a measured systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg. Diabetes was defined as a self-report of a physician diagnosis or a suspected diagnosis with current treatment, or as having a hemoglobin A1C (HbA1C) 6.5%. The assay used to determine HbA1C used the Tosoh HPLC G7 Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco CA) with non-fasting venous blood specimens. Cholesterol and high-density lipoprotein (HDL) cholesterol assays were performed using the Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) and non-HDL cholesterol was determined by subtracting the HDL value from the total cholesterol value. Body mass index (BMI) was calculated from measures of height and weight (kg/m^2) and obesity was defined as 30 kg/m^2.

Mean carotid intima-media thickness (IMT) and plaque score were determined through high resolution B-mode carotid artery ultrasound (MyLab25, Esaote North America Inc., Indianapolis, IN). The IMT was measured in 1.0 cm segments of the near and far walls of the common artery, internal artery and the carotid bifurcation. Ultrasound imaging and grading used a modified Atherosclerosis Risk in Communities protocol (Bond et al, 1991; Riley et al, 1991) and the mean of the 12 walls was calculated for the IMT measure. Mean IMT was categorized according to tertiles of the distribution as: 1) <= 0.6224 mm, 2) > 0.6224 mm and <= 0.7783 mm, 3) > 0.7783 mm. Plaque was considered to be present if acoustic shadowing was seen in association with at least one of the following, or if acoustic shadowing was not seen, with at least two of the following: change in wall shape (protrusion into lumen), change in wall texture, or IMT >1.5 mm. The plaque score was defined as the number of sites (0–6) with plaque present (Zhong et al, 2012; Schubert et al, 2015). Femoral pulse wave velocity (PWV) was measured using the Complior SP System (Artech Medical/ Alam Medical, Vincennes, France). The PWV from the right common carotid artery to the right femoral artery was measured at a time when the signal was clean, had a fast rising systole, sufficient systolic amplitude, a relatively flat diastole for at least 10 cycles, and when possible, a PWV tolerance <5% (Zhong et al, 2014; Schubert et al, 2015).

In EHLS participants, C-reactive protein (CRP) level was determined (Advanced Research and Diagnostic Laboratory, University of Minnesota, Minneapolis, MN) using a latex-

particle enhanced immunoturbidmetric assay from Roche Diagnostics on the Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) and was categorized into the following groups: <1.0 mg/L, 1.0–3.0 mg/L and >3.0 mg/L. Serum interleukin-6 (IL-6) was measured with the quantitative sandwich enzyme technique of enzyme-linked immunosorbent assay (QuantiKine High Sensitivity kit, R&D Systems, Minneapolis, MN) and was categorized into the following tertiles based on the distribution: <=1.192 pg/mL, > 1.192 and <= 2.252 pg/mL, >2.252 pg/mL. A summary measure of the number of inflammatory markers in the highest category was created (range: 0–2). Additional details of the CRP and IL-6 assays have been reported (Nash et al, 2013; Wichmann et al, 2014).

Self-reported smoking status was classified as non-smoker (<100 cigarettes in lifetime), ex-smoker, or current smoker. Alcohol consumption was measured by a quantity/frequency questionnaire and converted to grams of ethanol per week. Ever having consumed heavy alcohol was defined as ever drinking 4+ drinks per day. Exercise was defined as being sufficient to work up a sweat at least once a week.

Covariates

Demographic factors used in the analysis were age, sex, and education. Education was categorized as less than a high school graduate (<12 years), a high school graduate (12 years), some college (13–15 years), and college graduate or beyond (16+ years).

Handedness was determined by asking, "Are you right or left handed?' with possible answers of "Left", "Right", "Use both equally", or "Unknown". Cognition was measured with the Mini-Mental State Examination (MMSE) test (Folstein et al, 1975). The test was administered to participants aged 50 years and older; participants under the age of 50 were assumed to have no cognitive impairment. If the MMSE score was less than 24 (out of a maximum of 30), or if there was a self- or proxy-reported history of dementia or Alzheimer's disease, the subject was considered to have cognitive impairment.

Statistical Analyses

All analyses were completed using the SAS version 9.4 software (SAS Institute, Inc. Cary, NC).

General linear modeling was used to assess the age-sex adjusted associations of the categorically measured vascular health-related factors with the DDT-free recall total score and to estimate age-sex adjusted least squares means. Categorical covariates were modeled using indicator variables. To allow for estimates proportional to the observed margins, the ObsMargins (OM) option was used. Multiple linear regression was performed to evaluate the age-sex adjusted associations of the continuously measured factors with the DDT-free recall total score.

Multiple linear regression was used for multivariable modeling with the significant factors from the age-sex adjusted models included in the full multivariable model. The covariates previously identified as being significantly related to DDT-free recall total score, namely age, sex, education, hearing loss severity, and cognitive impairment (Fischer 2017), were also included in the multivariable model. Indicator variables were used in the models for the

education groups with the college graduate category as the reference group. Indicator variables were also used for the hearing loss severity groups with the no loss group as the reference. Cognitive impairment was a dichotomous variable. A final, reduced model was developed through the elimination of non-significant independent variables.

The modeling approach used for the DDT-free recall total score was followed for the right-left ear difference in percentage correct as the outcome.

RESULTS

The range of the free recall scores was 21.3% to 100% with a mean of 76.7%. Additional descriptive information on the study population and the distribution of the DDT scores has been reported (Fischer et al, 2017). In age- and sex-adjusted models, participants with a reported history of cardiovascular disease (CVD) had a mean total free recall score that was 2.0 percentage points lower (p < 0.01) than participants without CVD and those with diabetes had an average total free recall score that was 3.0 percentage points lower (p< 0.0001) than those without diabetes (Table 1). Hypertension was not strongly related to the total score. Obesity was significantly (p < 0.001) associated with the total DDT-free recall score whereby participants who were obese had a mean score 1.3 percentage points lower than the non-obese. Physical exercise was found to be related to a higher adjusted mean score (77.6% in those who exercised at least once/week vs 75.5% in those who did not; p < 0.0001) but smoking was not related. A history of heavy alcohol use was negatively associated (−1.9 percentage points) with DDT-free recall performance whereas current alcohol consumption was positively associated with performance (+0.19 percentage points in total score per 25 gram ethanol increase). The mean IMT, plaque count, non-HDL cholesterol and femoral PWV were not significantly associated with performance.

In a multivariable model, diabetes was associated with a lower DDT-free recall score (−2.08 percentage points, p < 0.001) (Table 2). Alcohol consumption and exercise were associated with higher DDT-free recall scores (+0.15 percentage points per +25 grams ethanol and +1.07 percentage points if exercise at least once/week, p < 0.01 for each). CVD history and obesity were no longer significantly related to DDT-free recall score in the multivariable models. However, if diabetes was removed from the multivariable model, CVD history was significant (−1.64 percentage points, p= 0.01) and obesity was close to significant (−0.70 percentage points, p = 0.06). No significant relationship was observed in the EHLS participants between DDT-free recall total score and high levels of CRP and IL-6 (age-sex adjusted mean score by number of high markers: 0 = 71.6%, 1 = 72.3%, 2 = 71.4%; p = 0.60). If a history of heavy alcohol use was included in the multivariable model in place of current alcohol consumption, it was not significantly related to the total DDT-free recall score (p = 0.15).

The overall mean right-left ear difference, or REA, in DDT-free recall scores was 14.7 percentage points (Table 3). Information on the distribution of the right-left ear difference in DDT scores has been previously reported (Fischer et al, 2017). In age-sex adjusted models, CVD, diabetes, and a history of heavy alcohol use some time in the past were significantly associated with a greater adjusted mean right-left ear difference (CVD: +2.5 percentage

points, p = 0.03; diabetes: +3.3 percentage points, p < 0.001; heavy alcohol use: +1.9 percentage points, p = 0.03). Non-HDL cholesterol (−0.21 percentage points per +10 mg/dL, p = 0.02) and femoral PWV (+0.36 percentage points per 1 m/s, p < 0.01) were also significantly related to the right-left ear difference in DDT-free recall scores. Hypertension, obesity, smoking, exercise, mean IMT, plaque, and weekly alcohol consumption were not associated with the difference. In a multivariable model, effect estimates were similar to those in the age-sex adjusted models (CVD: + 3.11 percentage points, p = 0.02; non-HDL cholesterol: −0.22 percentage points per 10 mg/dL, p = 0.01; femoral PWV: +0.36 percentage points per 1 m/s, p < 0.01). However, diabetes and heavy alcohol use were no longer significant. Adjustment for handedness altered the effect estimates very little (CVD: + 3.04 percentage points, p = 0.02; non-HDL cholesterol: −0.22 percentage points per 10 mg/dL, p = 0.01; femoral PWV: +0.37 percentage points per 1 m/s, p < 0.01).

DISCUSSION

Associations between vascular health-related factors and the DDT-free recall total score and right-left ear difference were observed in this cross-sectional study suggesting that vascular health and central auditory function may be connected. Diabetes was associated with lower DDT-free recall total scores whereas exercise and alcohol consumption were associated with higher total scores. Effects were modest in size and although statistically significant, they may not be clinically significant. However, in previous cross-sectional work in the same study cohort, a difference of −1% in the DDT total free recall score was observed for every +5 years of age (Fischer et al, 2017). Therefore, the diabetes effect found in the present study could be thought of as roughly equivalent to +10 years of age whereas the exercise effect could be thought of as roughly equivalent to −5 years of age. Cardiovascular disease history and a greater femoral PWV were significantly related to a greater right-left ear difference in free recall scores. These relationships were independent of any confounding effects of age, sex, education, hearing loss severity, and cognitive impairment.

It has been suggested that auditory perception and speech communication are dependent on the interaction between hearing function, central auditory processing, and cognitive function (Humes et al, 2012). Therefore, performance on tests of speech-in-noise or dichotic listening is likely dependent on all three of these functions. Although vascular health-related factors have been found to be associated with auditory thresholds and cognitive function in previous studies, the current study adds to these findings by focusing on a central auditory processing test. Adjustments for the effects of hearing loss severity and cognitive impairment were made to evaluate the independent relationships of the vascular factors with central auditory processing.

Previous studies reporting a relationship of vascular health-related factors with hearing function, change, and impairment, using audiometric threshold measures have included prospective (Kiely et al, 2012; Nash et al, 2014; Linssen et al, 2014; Cruickshanks et al, 2015; Fischer et al, 2015) and cross-sectional investigations (Gates et al, 1993; Cruickshanks et al, 1998a; Bainbridge et al, 2008; Helzner et al, 2011). Among the findings from these studies was a report that high glycosylated hemoglobin (GHb > 12%) was related to a two-fold increased risk of hearing impairment over a 15-year follow-up (Cruickshanks et al,

2015). However, there was not a significant association of hearing impairment risk with diabetes (self-reported doctor-diagnosis or a GHb > 8%) or with other levels of GHb; the increased risk was confined to those with high GHb. A cross-sectional study using self-reported doctor-diagnosed diabetes found that individuals with diabetes had an 80% increased likelihood of having a hearing impairment in the low-mid frequencies and were over twice as likely to have a high frequency impairment (Bainbridge et al, 2008). Adjustment for cardiovascular, inflammatory, and neuropathic factors attenuated these relationships although they remained significant (Bainbridge et al, 2010). A third study, a case-control study of type 2 diabetes, found that controls had significantly shorter suprathreshold gap detection thresholds and lower speech thresholds than cases in the Hearing in Noise Test with background noise (Frisina et al, 2006). It is noteworthy that performance on these two tests is dependent not only on auditory thresholds but also on central auditory processing. The current study supports these findings as it also found higher DDT scores among participants without diabetes.

The present study also found that exercise and alcohol consumption were associated with higher DDT-free recall scores. Research has been conducted investigating possible protective effects of physical activity (Paffenbarger et al, 1978; Folsom et al, 1997; Jakovljevic, 2017) and moderate alcohol consumption (Friedman and Kimball, 1987; Fuchs et al, 1995; Lucas et al, 2005) on vascular health-related conditions and events for many years but physical activity and alcohol consumption have generally not been widely studied in relation to hearing loss. In previous work related to physical activity, it has been reported that participants who exercised at least once per week had a slightly (-1 dB), but significantly, lower $PTA_{0.5,1,2,4 \text{ kHz}}$ at a 5 year follow-up exam (Fischer et al, 2015). In addition, in a study of self-reported hearing problems, higher physical activity has been found to be protective (Curhan et al, 2013). In two prospective investigations, alcohol consumption was not found to be significantly related to hearing impairment risk (Cruickshanks et al, 2015; Fischer et al, 2015).

The concept of an REA in dichotic listening tests (Kimura, 1961), in which performance is better for material presented to the right ear than the left ear, has been previously studied but little work has been done investigating factors related to the REA other than age and handedness. The hypothesized explanation for the REA is that through the crossed afferent auditory pathway, the right ear is linked to the left hemisphere of the brain which specializes in verbal processing. Since the left ear signals are routed to the right hemisphere, interhemispheric transfer through the corpus callosum must take place for recognition of verbal stimuli from the left ear. With age and possible age-related neurodegeneration, this transfer may become less effective in a dichotic listening situation (Jerger et al, 1995; Greenwald and Jerger, 2001). A greater REA has been found in older ages (Wilson and Jaffe, 1996; Strouse and Wilson, 1999a, 1999b; Roup et al, 2006; Fischer et al, 2017) perhaps as a result of a more pronounced age effect on left ear performance than right ear performance.

Recently, a greater REA was found to be related to lower education level and the presence of cognitive impairment (Fischer et al, 2017) which is compatible with early findings suggesting that as the difficulty of the task increases, the REA increases (Strouse and

Wilson, 1999a, 1999b). In the present study, a greater REA was associated with CVD history and higher femoral PWV, a measure of arterial stiffness, findings which are in line with previous work evaluating the relationship between these measures and cognitive functioning. Greater carotid artery IMT, a measure of generalized atherosclerosis, was found to be associated with an increased risk of cognitive impairment over 10 years (Zhong et al, 2012) and a higher Framingham cardiovascular disease risk score was reported to be related cross-sectionally to lower cognitive test performance in both sexes and prospectively to cognitive decline in men (Kaffashian et al, 2011). A negative association between femoral PWV and cognitive function has been reported whereby a PWV > 12 m/s was associated with lower cognitive test scores (Zhong et al, 2014). Other studies, including prospective investigations, have reported a similar negative association with at least some cognitive tests (Waldstein et al, 2008; Mitchell et al, 2011; Watson et al, 2011) although not all have found significant associations (Poels et al, 2007).

The observed relationships in the current study and previous work may be a result of the potential impact of microvascular changes such as small vessel damage and of various pathophysiologic changes accompanying vascular disease including reduced blood flow. For example, internal auditory artery narrowing and demyelination of the eighth cranial nerve along with thickening of the capillaries in the stria vascularis and spiral ganglion atrophy have been found in autopsied diabetic subjects (Bainbridge et al, 2010). The state of hyperglycemia may impact the central nervous system as well as the inner ear (Frisina et al, 2006) and the oxidative damage, greater apoptosis, and disruption of metabolic processes that accompanies prolonged hyperglycemia may result in neurodegenerative damage. In contrast, regular physical activity may be beneficial for auditory function through mechanisms such as improved endothelial function and reduced oxidative stress and may provide neuroprotective effects on central auditory processing (Curhan et al, 2013). For example, regular physical activity has been shown to be associated with lower aortic PWV (less stiffening) (Vaitkevicius et al, 1993; Tanaka et al, 1998) perhaps as a result of reduced oxidative stress (Seals et al, 2009). The physiologic consequences of arterial stiffness include reduced blood flow to the brain and small vessel damage (O'Rourke and Safar, 2005).

This study's strengths include the large size (n=3655) of the study population and the wide age range of the participants (nearly 80 year age span). Information on numerous vascular health conditions and measures were available for evaluation. Similar protocols were followed by trained and certified examiners in the EHLS and the BOSS so data from the two cohorts could be combined. The test-retest reliability of the DDT has been shown to be good (Strouse and Wilson, 1999a) although the methodology used in the reliability assessment randomly presented one-, two-, and three-digit pair modalities which is a departure from the methodology used in the present study and the participants were on average younger (mean age = 49.4 years) with a larger percentage of males (72%) than in the present study. Although much of the previous work with dichotic listening tests have evaluated ear-specific function, the total of the right and left ear DDT scores was used as one of the outcomes in the current study. The objective of the study was to investigate the relationship between vascular health-related factors and DDT performance on a population level. The total score was a comprehensive measure of overall performance. With respect to limitations, the study

was cross-sectional; therefore temporal relationships cannot be inferred. The significant factors found to be related to the DDT-free recall total score and the right-left ear difference were not the same in the present study but this lack of consistency may be a reflection of the different aspects of central auditory processing that they each measure. The DDT-free recall total score provides a summary measure of DDT performance. In contrast, as a difference measure, the right-left ear difference does not include information on how well participants performed. For example, one participant could have scored 95% in the right ear and 90% in the left ear and another participant could have scored 75% in the right ear and 70% in the left ear; both participants had a right-left ear difference of 5% but they performed very differently on the test. Therefore, the DDT-free recall total score was evaluated to determine factors associated with overall central auditory processing function. The right-left ear difference was evaluated to determine factors associated with the right-ear advantage without regard to performance level. The difference in findings between the total score and the right-left ear difference with respect to CVD history may also be related to the possibility that CVD and diabetes share a common effect on the DDT-free recall total score; CVD history was significant when diabetes was not included in the multivariable modeling. Finally, although the DDT-right ear directed recall was administered, there was not sufficient variability in performance to allow for the investigation of vascular health-related factors.

The present study found a relationship of a number of vascular health-related factors with performance on the DDT-free recall. Relationships were found when evaluating the DDT-free recall total score as well as the right-left ear difference in the DDT-free recall scores. These results suggest that vascular health-related factors, including modifiable behaviors, may play a role in central auditory function and these factors should be considered as possible predictors of central auditory decline or dysfunction in future prospective investigations.

Acknowledgments

ABBREVIATIONS

BDES	Beaver Dam Eye Study
BMI	body mass index
BOSS	Beaver Dam Offspring Study
CRP	C-reactive protein
CVD	cardiovascular disease
dB	decibel
DDT	Dichotic Digits Test

EHLS	Epidemiology of Hearing Loss Study
HbA1C	hemoglobin A1C
HDL	high-density lipoprotein
HL	hearing level
GHb	glycosylated hemoglobin
IL-6	interleukin-6
IMT	intima-media thickness
MMSE	Mini-Mental State Examination
PTA	pure-tone average
PWV	pulse wave velocity
REA	right ear advantage

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Table 1

Free Recall Dichotic Digits Test Score (%) Age-Sex Adjusted Means by Potential Related Factors

	N (%)	Free Recall (%)	
		Mean	p-value[†]
Overall	**3655 (100.0)**	**76.7**	**-**
Categorically Measured Factors			
Cardiovascular Disease History			< 0.01
Yes	343 (9.4)	74.9	
No	3294 (90.6)	76.9	
Hypertension			0.24
Yes	1888 (51.9)	76.5	
No	1752 (48.1)	77.0	
Diabetes			< 0.0001
Yes	512 (14.0)	74.1	
No	3135 (86.0)	77.1	
Obesity (Body Mass Index >=30.0)			< 0.001
Yes	1785 (49.9)	76.1	
No	1791 (50.1)	77.4	
Smoking Status			0.40
Never	1882 (51.6)	76.7	
Former	1351 (37.0)	76.8	
Current	416 (11.4)	76.0	
Ever Heavy Alcohol			< 0.001
Yes	731 (20.5)	75.1	
No	2836 (79.5)	77.0	
Exercise at Least 1x/wk			< 0.0001
Yes	2025 (55.5)	77.6	
No	1622 (44.5)	75.5	
Mean Intima-media Thickness (tertiles)			0.24
1	1201 (33.3)	76.3	

	N (%)	Free Recall (%)	
		Mean	p-value[†]
Overall	**3655 (100.0)**	**76.7**	**-**
2	1204 (33.4)	77.2	
3	1201 (33.3)	76.9	
Plaque Count			0.26
0	1536 (43.5)	77.1	
1–3	1618 (45.8)	76.9	
4–6	377 (10.7)	75.9	
Continuously Measured Factors			
	Mean (S.D.)	Free Recall (%)	
		β	p-value
Alcohol Consumption/Week (β: per 25 gm)	50.8 (95.1)	0.19	< 0.001
Non-HDL Cholesterol (β: per 10 mg/dL)	143.5 (39.1)	0.08	0.11
Pulse Wave Velocity - Femoral (β: per 1 m/s)	9.8 (2.7)	−0.03	0.68

Table 2

Free Recall Dichotic Digits Test Score (%) Multivariable-Adjusted Linear Regression Models[1]

	Free Recall Dichotic Digits Test Score (%)					
	Full (n=3538)			Reduced (n=3627)		
	B (%)	Standard Error	p-value	β	Standard Error	p-value
Cardiovascular Disease History	−1.06	0.66	0.11	-	-	-
Diabetes	−1.66	0.57	< 0.01	−2.08	0.54	< 0.001
Obesity	−0.52	0.38	0.17	-	-	-
Exercise at Least 1x/week	1.05	0.38	< 0.01	1.07	0.38	< 0.01
Alcohol Consumption/Week (per 25 grams)	0.15	0.05	< 0.01	0.15	0.05	< 0.01

[1] Also includes adjustment for age, sex, education, hearing loss severity, and cognitive impairment

Table 3

Right Ear Minus Left Ear Free Recall Dichotic Digits Test Scores (%) Age-Sex Adjusted Mean Difference by Potential Related Factors

	Free Recall Right-Left Ear Difference (%)	
	Mean	p-value[†]
Overall	**14.7**	**-**
Categorically Measured Factors		
Cardiovascular Disease History		0.03
Yes	16.9	
No	14.4	
Hypertension		0.39
Yes	14.9	
No	14.3	
Diabetes		< 0.001
Yes	17.5	
No	14.2	
Obesity (Body Mass Index >=30.0)		0.20
Yes	15.1	
No	14.2	
Smoking Status		0.55
Never	14.4	
Former	15.1	
Current	14.3	
Ever Heavy Alcohol		0.03
Yes	16.2	
No	14.3	
Exercise at Least 1x/wk		0.61
Yes	14.5	
No	14.9	
Mean Intima-media Thickness (tertiles)		0.56

	Free Recall Right-Left Ear Difference (%)	
	Mean	p-value[†]
Overall	**14.7**	**-**
1	15.3	
2	14.5	
3	14.2	
Plaque Count		0.96
0	14.7	
1–3	14.7	
4–6	14.3	

Continuously Measured Factors		
	Free Recall Right-Left Ear Difference (%)	
	β	p-value
Alcohol Consumption/Week (β: per 25 gm)	−0.04	0.65
Non-HDL Cholesterol (β: per 10 mg/dL)	−0.21	0.02
Pulse Wave Velocity - Femoral (β: per 1 m/s)	0.36	< 0.01

Table 4

Right Ear Minus Left Ear Free Recall Dichotic Digits Test Scores (%) Multivariable-Adjusted Linear Regression Models[1]

| | Free Recall Right-Left Ear Difference (%) | | | | | |
| | Full (n=3261) | | | Reduced (n=3339) | | |
	B (%)	Standard Error	p-value	β	Standard Error	p-value
Cardiovascular Disease History	3.04	1.31	0.02	3.11	1.28	0.02
Diabetes	1.22	1.07	0.25	-	-	-
Ever Heavy Alcohol	0.78	0.90	0.39	-	-	-
Non-HDL Cholesterol (per 10 mg/dL)	−0.23	0.09	0.01	−0.22	0.09	0.01
Pulse Wave Velocity - Femoral (per 1 m/s)	0.35	0.14	0.01	0.36	0.14	< 0.01

[1] Also includes adjustment for age, sex, education, hearing loss severity, and cognitive impairment