1.a. Full Title: Cross-sectional Association of Hearing Impairment and Region-Specific Brain Volumes in the Atherosclerosis Risk in Communities Hearing Pilot Study

b. Abbreviated Title (Length 26 characters): Hearing and Brain MRI

2. Writing Group: (Alphabetical): Josh Betz, Jennifer A. Deal (first author), Rebecca Gottesman, Clifford R. Jack, Frank R. Lin (senior author), Melinda Power, Susan Resnick, A. Richey Sharrett

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JAD [please confirm with your initials electronically or in writing]

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3. Timeline:
Manuscript will be completed in 6 months.

4. Rationale:
Two converging lines of evidence suggest that hearing impairment and alterations in peripheral auditory function could directly or indirectly lead to central effects on brain structure and function. Cross-sectional neuroimaging studies have demonstrated that peripheral hearing impairment (HI) is associated with reduced cortical volumes in the primary auditory cortex and variation in the integrity of central auditory white matter tracts. The basis of these associations remains unknown but may be related to alterations in the degree of neural activation provided by an impoverished auditory signal, leading to subsequent structural changes in cortical reorganization and brain morphometry. Interestingly, degradation in the fidelity of peripheral encoding of sound likely results in recruitment and activation of broader neural networks for auditory processing, suggesting that peripheral hearing impairment may carry cascading negative consequences for other brain regions.

Epidemiologic studies suggest an association between HI and cognitive function. In these studies of older adults, peripheral HI was independently associated with poorer neurocognitive
performance on both auditory and non-auditory tests, \(^9-^{13}\) accelerated rates of cognitive decline, \(^{14}\) and increased risk of incident all-cause dementia. \(^{15,16}\) Hypothesized mechanisms to explain these associations include a shared neuropathologic etiology, cognitive load from the reallocation of brain resources for auditory processing, \(^{17,18}\) and/or and effect of hearing loss on cognition through social isolation. \(^{19,20}\)

Whether peripheral hearing impairment is associated with atrophy of regions outside the primary auditory cortex and with brain volumes remains poorly studied. Only one manuscript published recently using longitudinal data from the Baltimore Longitudinal Study of Aging (BLSA) has appreciably studied the association of hearing impairment with size of brain regions outside the auditory cortex. \(^{21}\) This study demonstrated that hearing impairment was associated with accelerated longitudinal atrophy in whole brain and right superior, middle, and inferior temporal gyri over a median 6 years of follow-up. Interestingly, cross-sectional results (in contrast to longitudinal results) were not significant in this study, possibly suggesting that substantial interindividual heterogeneity in brain volumes may limit the ability to detect modest associations between HI and brain volumes in cross-sectional analyses.

5. **Main Hypothesis/Study Questions:**

The goal of the present investigation is to pilot analyses of the cross-sectional association of HI with region-of-interest brain volumes at ARIC Visit 5. While we do not expect statistical significance given the small sample size of this pilot analysis, we hypothesize that there is a trend toward HI being weakly associated with regional brain volumes in the lateral temporal lobe consistent with cross-sectional results from the BLSA. We will also explore the association of HI with total white matter hyperintensities, and we hypothesize that a weak positive association will be present. These “exploratory” analyses will represent the largest cross-sectional analyses of hearing and MRI data published to date in the extant literature. Understanding the association of hearing impairment with structural brain volumes may provide insights into mechanistic pathways through which peripheral impairments in sensory function could contribute to brain aging and will serve as a prelude to other possible HI-MRI analyses in ARIC.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study design:** Cross-sectional observational study of 155 men and women who underwent audiometric hearing testing (Washington County site only) and brain MRI at Visit 5. Participants were excluded from the MRI study at Visit 5 given presence of tumor, surgery or radiation to the head/brain, or multiple sclerosis.

**Outcome:**
Freesurfer was used to segment images and place regions of interest (ROI). Gross anatomical regions were taken as the sum of their constituent subregion ROIs:

- **Frontal Lobe:** lateral orbitofrontal cortex, medial orbitofrontal cortex, paracentral gyrus, pars opercularis, pars orbitalis, pars triangularis, precentral gyrus, rostral anterior cingulate, rostral middle frontal gyri, superior frontal gyri, and frontal poles
- **Parietal Lobe:** inferior parietal lobule, isthmus of the cingulate gyrus, postcentral gyrus, posterior cingulate, precuneus, superior parietal lobule, and supramarginal gyrus
- **Occipital Lobe:** cuneus, lateral occipital lobule, lingual gyrus, and pericalcarine cortex
- **Temporal Lobe**: banks of the superior temporal sulcus, entorhinal cortex, fusiform gyri, inferiortemporal gyri, middletemporal gyri, parahippocampal gyri, superior temporal gyri, temporal poles, transverse temporal gyri, hippocampus, and amygdala
- **Deep Gray & White Matter**: insula, thalamus, caudate, putamen, and globus pallidus

**Exposure**: Pure tone air conduction audiometry and speech perception testing were conducted at Visit 5 in a sound-treated booth within a quiet room. Using that data, we will calculate the following hearing impairment variables:

1. **Pure tone air conduction audiometry (a measure of the auditory periphery):**
   - **Pure tone average (PTA)**. Pure tone audiometry is the gold-standard test to determine the faintest tones that a person can detect for a range of pitches. We will calculate a speech frequency PTA using audiometric thresholds at 0.5, 1, 2, and 4 kHz in the better-hearing ear in accordance with the World Health Organization definition of hearing loss. The primary analysis for PTA will categorize hearing loss as a PTA exceeding 25 dB. In secondary analyses, we will test for possible dose-response relationship between hearing impairment and brain volumes using a clinically defined ordinal variable for hearing impairment (normal: <25 dB, mild: 26-40 dB, moderate: 41-70 dB, severe: >70 dB). Additionally, we will utilize PTA as a continuous variable to determine if there is a linear relationship with brain volumes, and within the clinically defined categories defined above.

2. **Speech perception testing (a measure of central auditory processing):**
   - **Signal to noise (SNR) ratio loss**. In this study, SNR loss was measured using the *Quick Speech In Noise (QuickSIN)* test, which quantifies a participant’s ability to hear and repeat speech in an increasingly noisy environment. A pre-recorded list of 6 sentences containing 5 key words per sentence was played at 70 dB for the participant; each sentence was contained within a recording of four-talker babble with an increasing SNR (25, 20, 15, 10, 5 and 0, respectively). SNR Loss was calculated as 25.5 – (Total number of key words correctly repeated). Two trials (of 6 sentences) were conducted; an average of the two trials will be used for the analysis.

**Additional independent variables**:
Demographic information was collected at Visit 1, including age (years), and sex. Audiometric testing at Visit 5 was limited to Washington County, Maryland. Because of the small number of non-white participants (N=1 Asian and N=1 Black), the analysis will be restricted to participants self-reporting white race.

Disease covariates were collected at each study visit, and adjudicated according to standardized algorithms. **Hypertension** will be considered present based on a diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥140 mmHg, or use of hypertensive medications. **Diabetes** will be considered present if fasting blood glucose level was ≥ 126 mg/dL, or the participant self-reported a diagnosis of diabetes or of medication use for diabetes.

Self-reported hearing aid use and duration of use was collected at Visit 5. Hearing aid use will be defined self-reported hearing aid use in either ear during the previous month based on the following two questions:

"*Do you currently use a hearing aid in your right (left) ear?*"

If Yes, "*Averaged over the past month, about how many hours per day have you worn your hearing aid in the right (left) ear?*"
Statistical analysis:
Differences in demographics and cardiovascular risk factors will be compared using the Kruskal-Wallis Test and Fisher’s Exact Test in unweighed analyses, and using ANOVA and Chi-square using survey weights to account for the sampling design. Multiple linear regression will be performed with survey weights, in keeping with current recommendations from the MRI working group. Linearity of associations between imaging volumes will be assessed using component-residual plots. Analyses will be adjusted for age, sex, total intracranial volume, and for cardiovascular risk factors associated with hearing loss, including diabetes and hypertension.

References


7.a. Will the data be used for non-CVD analysis in this manuscript?
____ Yes  __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  N/A
____ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
____ Yes  __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  N/A
____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  http://www.cscc.unc.edu/ARIC/search.php
____X__ Yes  ________ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP2315. Schneider et al. Association of Diabetes with Brain Magnetic Resonance Imaging

MP 2327. Deal et al. Hearing impairment and cognitive performance in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC NCS): cross-sectional and longitudinal results

MP 2351. Power et al. Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____Yes  ___ X  ___No

11.b. If yes, is the proposal N/A
    1. A. primarily the result of an ancillary study (list number* __________)
    2. B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a **Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.