ARIC Manuscript Proposal #H3741

PC Reviewed: 11/16/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Cross-sectional associations of peripheral hearing, brain magnetic resonance imaging (MRI) measures and cognitive performance with speech-in-noise performance in community-dwelling older adults

b. Abbreviated Title (Length 26 characters):
PTA, MRI, cognition and QuickSIN

2. Writing Group:
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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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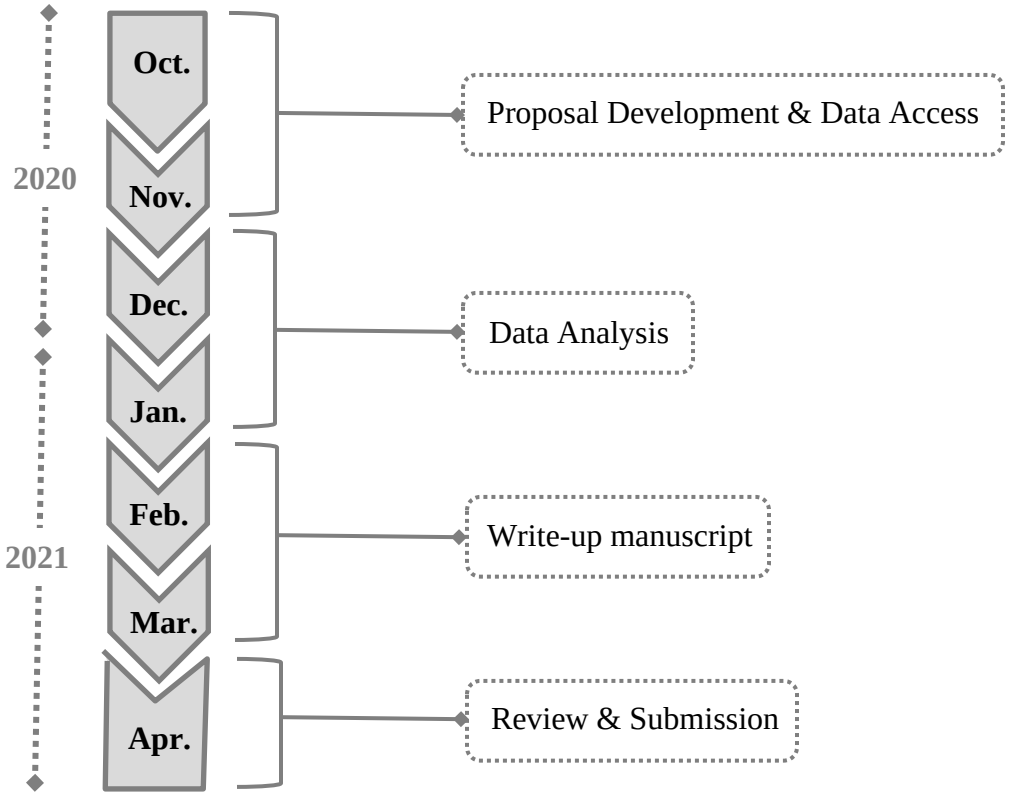
3. Timeline:



4. Rationale:

Difficulty understanding speech in the presence of noise is prevalent among older adults.[1] Speech understanding in noise is fundamental to daily lives since it impacts communication and relationships. When understanding is impaired, this can potentially lead to feelings of isolation.[2] Additionally, speech understanding in noise is related to older adults' subjective awareness of hearing difficulties as well as cognitive efforts needed to understand messages.[3]

Speech understanding involves both bottom-up and top-down processes.[4] Bottom-up processing is data-based; sound waves travel through the ear and are transformed into electrical impulses in the peripheral auditory system and then are transmitted via the auditory nerve ascending to the auditory region of the brain located in the superior temporal lobe.[5,6] Top-down processing, however, is knowledge-based and involves cognitive processes.[6] Older adults with difficulty in speech understanding may face challenges in both bottom-up and top-down

processes, where input of auditory signals are degraded and decoding of auditory signals are compromised.[7,8]

Prior studies have proposed three hypotheses regarding mechanisms of speech-understanding difficulties among older adults: (1) peripheral auditory system dysfunction; (2) central auditory system dysfunction; (3) cognitive deficits.[9,10] Evidence is lacking, especially regarding the top-down processing of speech understanding. Studies investigating the contribution of cognitive processes to speech-in-noise performance have generally had small sample sizes, a limited neurocognitive test battery, and a lack of comprehensive brain imaging data.[7,11,12]

ARIC is uniquely poised to address these research gaps given its comprehensive measures, including peripheral hearing, brain imaging, and neurocognitive data in a large cohort of older adults, and will contribute significantly to the existing limited body of literature. The identification of measures of neurocognitive function and brain structures that are associated with speech-in-noise performance may inform interventions among older adults with hearing loss.

5. Main Hypothesis/Study Questions:

Study Question:

To investigate cross-sectional associations of peripheral hearing, brain MRI measures and cognitive function with speech-in-noise performance among older adults aged 70-84 years with mild to moderate hearing loss at ACHIEVE baseline (2018-2019) and ARIC-NCS participants at Visit6/Visit 7 (2017-2019) with comparable age, cognitive status, and functional status as ACHIEVE participants.

Main Hypothesis:

Worse speech-in-noise performance (i.e., lower scores) measured by Quick Speech-in-noise (QuickSIN) test are independently associated with the following exposures:

- Worse peripheral hearing measured by audiometry [higher pure tone average (PTA)]
- Smaller volumes of temporal lobe regions of interest (ROI) involved in the processing of auditory signals, particularly the superior temporal lobe
- Greater volumes of white matter hyperintensities (WMH)
- Poorer white matter integrity measured by diffuse tensor imaging (DTI), including lower fractional anisotropy (FA) and higher mean diffusivity (MD)
- Poorer neurocognitive test performance (lower scores)

Focus of this Proposal: This proposed work is part of the ACHIEVE MRI Ancillary grant (R01AG060502). Given the focus of that grant, this proposal will be limited to investigating the role of audiometric hearing, brain MRI measures and cognition on speech-in-noise performance. Although the relationship of these variables with cognitive performance as the outcome is of interest, a separate manuscript proposal will be submitted to address that research question.

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 analysis of baseline ACHIEVE participants and V6/V7 ARIC-NCS participants to investigate the impact of peripheral hearing, brain MRI measures and cognitive tests scores on speech-in-noise performance.

Study Population:

- Baseline (2018-2019) participants aged 70-84 years with mild to moderate hearing loss recruited into the ACHIEVE study meeting the study's inclusion and exclusion criteria.[13]
- ARIC-NCS participants at Visit6/Visit 7 (2017-2019) who have comparable age, cognitive status and functional status per ACHIEVE inclusion/exclusion criteria. All ACHIEVE participants will have mild to moderate hearing loss. ARIC participants will include a wider range of hearing, including normal hearing and severe hearing loss.

Outcome:

Speech-in-noise performance was quantified by the QuickSIN test.[14] Total scores range from 0 to 30 with higher scores indicating better speech-in-noise performance.

Exposure:

Peripheral Hearing	Pure tone average (PTA) in the better-hearing ear	The average of hearing thresholds at 0.5, 1, 2 and 4 kHz, with higher values indicating worse peripheral hearing. Right-ear and left-ear PTAs will both be investigated with better-ear PTA used in primary analysis. PTAs will be categorized according to clinical cut points: normal hearing [<25 decibels hearing level (dB HL)]; mild (26-40 dB HL); moderate (41-60 dB HL); severe (61-80 dB HL) and profound (>80 dB HL) hearing loss.[15]
Brain MRI Measures	Volumes of regions of interest (ROI) in cm^3	Primary ROIs for inference include the temporal lobe and superior temporal lobe, the location of the primary auditory cortex.[16,17] We will model brain volumes as standardized continuous variables
	Volume of white matter hyperintensities (WMH) in cm^3	We will model volume of WMH continuously.
	Fractional anisotropy (FA) and mean diffusivity (MD) of white matter tracts derived from diffuse tensor imaging (DTI)	FA is a continuous measure of directional constraint of water diffusion ranging from 0 to 1, with lower values indicating worse white matter (WM) integrity.[18] MD is a continuous measure of the rate of water diffusion (mm^2/s), with higher values indicating worse WM integrity.[18]

Cognitive Test Scores	o Delayed Word Recall Test o Logical Memory o Incidental Learning o Trail Making Test Part A o Trail Making Test Part B o Digit Symbol Substitution Test o Digit Span Backward o Boston Naming Test o Animal Naming o Word Fluency	For inference, we will primarily consider tests of executive function. Continuous scores will be standardized to z-scores. For ARIC participants, we will use cognitive data collected at V6, the same time as the hearing measures.

Other Covariates:

- Demographic variables: age, sex, race-center, education, APOE ε4;
- Lifestyle variables: smoking, body mass index (BMI);
- Cardiovascular diseases variables: hypertension, diabetes, coronary heart disease, stroke;
- Brain measures: intracranial volume.

Statistical Analysis:

Multivariable-adjusted linear regression will be used with QuickSIN score as the outcome. Separate models will be run for each of the main exposures, including levels of peripheral hearing loss, brain MRI measures and standardized cognitive test scores. A combined model investigating the relative contribution of each exposure will also be run. Potential interactions between main exposures will be explored. Models will adjust for age, sex, race-center, education, APOE ε4, smoking, BMI, hypertension, diabetes, coronary heart disease, stroke and intracranial volume. We will explore non-linear relationship between continuous measures and the outcome, and splines will be used if non-linearity exists. Model fit will be assessed by diagnostic tests and plots.

Limitations:

Because this proposal will use data from both ARIC and ACHIEVE, we are limited to a cross-sectional analysis. However, in the subset of participants in both ARIC and ACHIEVE, we will be able to look at prior trajectory of cognitive change as our exposure in a sensitivity analysis.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __ X __ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ 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/mantrack/maintain/search/dtSearch.html

___ 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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ____ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* _2016.03**_)**

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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