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Clinician-judged hearing impairment and associations with neuropathologic burden

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Abstract

Objective

To examine whether neuropathologic burden is associated with hearing impairment.

Methods

We studied 2,755 autopsied participants ≥ 55 years of age from the National Alzheimer's Coordinating Center database. Participants had at least 1 clinical evaluation at US National Institute on Aging–funded Alzheimer's Disease Center no more than 2 years before death. Patients were classified as hearing impaired by clinician report at baseline. Common dementia neuropathologies included Alzheimer disease pathologic change (Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque density, neurofibrillary degeneration Braak stage), Lewy body disease, gross infarcts, and microinfarcts. Logistic regression models predicted impaired hearing with adjustment for age at death, sex, race, education, center, and follow-up time. Relative risks were calculated with the use of marginal standardization.

Results

Impaired hearing was common (32%). In participants who were cognitively normal at baseline ($n = 580$), impaired hearing was associated with higher Braak stage (relative risk [RR] 1.33 per 2-stage increase, 95% confidence interval [CI] 1.06–1.66) but not other pathologies. In participants with dementia ($n = 2,175$), impaired hearing was positively associated with microinfarcts (RR 1.18, 95% CI 1.00–1.39) and inversely associated with neuritic plaque density (RR 0.91 per score increase, 95% CI 0.85–0.99). Development of impaired hearing in those with cognitive impairment was associated with neocortical Lewy bodies (1.26, 95% CI 1.02–1.55).

Conclusions

Impaired hearing, reported before the onset of cognitive impairment, was associated with increased neurofibrillary tangle burden. Impaired hearing in those with cognitive impairment was associated with microinfarcts and neocortical Lewy bodies but not typical Alzheimer disease pathologic change. Functional hearing problems may be a preclinical marker of neurofibrillary neurodegeneration, although replication is needed.

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Editorial

Age-related hearing loss and neuropathologic burden: A step inside the cognitive ear

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Glossary

AD = Alzheimer disease; **ADC** = Alzheimer's Disease Center; **ADNC** = AD neuropathologic change; **CDR-SB** = Clinical Dementia Rating Dementia Staging Instrument Sum of Boxes; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **FTLD** = frontotemporal lobar degeneration; **NACC** = National Alzheimer's Coordinating Center; **PART** = primary age-related tauopathy; **RR** = relative risk; **TDP-43** = TAR DNA-binding protein 43; **UDS** = Uniform Data Set; **VBI** = vascular brain injury.

Emerging evidence suggests that age-related hearing impairment is associated with increased risk of dementia.¹⁻⁶ Multiple biological mechanisms have been posited to explain this association, but it is unclear whether hearing impairment is associated with a specific pattern of neurodegenerative disease neuropathology. Hearing impairments can be caused by degradation in peripheral structures in the inner ear or central auditory processing dysfunction in brain.^{7,8} Impaired hearing could indirectly accelerate cognitive decline through effects on social isolation or reduced cognitive reserve.^{7,9,10} Alternatively, underlying neurodegeneration associated with dementia may affect central auditory processing and cause difficulty hearing.^{8,11,12} However, hearing impairment may increase misclassification of cognitive impairment,¹³⁻¹⁵ in which case dementia-causing pathologies would be less common in individuals with compared to those without hearing impairment. Hearing loss is associated with structural volumes in some studies,¹⁶⁻¹⁸ but it is not established whether specific neuropathologic changes are linked to hearing impairment. Such research may help disentangle mechanisms and is important to understanding whether hearing loss is a relevant target for dementia prevention or preclinical detection.

The objective of this study was to use data from one of the largest autopsy samples, the National Alzheimer's Coordinating Center (NACC) database, to examine whether neuropathologic profiles differ between those with and those without clinician-reported hearing impairment. We focus on common neuropathologies of aging related to Alzheimer disease (AD), Lewy body disease, vascular brain injury (VBI), and primary age-related tauopathy (PART). We compare findings between those with and those without cognitive impairment at the time of reported hearing function.

Methods

Standard protocol approvals, registrations, and patient consents

Individual Alzheimer's Disease Centers (ADCs) received institutional review board approval, and written informed consent was obtained from all participants and their study coparticipants. NACC received institutional review board approval from the University of Washington for release of deidentified data.

Data sources and study populations

NACC participants were prospectively evaluated at 1 of ≈ 30 US ADCs between September 2005 and September 2018.

Each ADC recruits and enrolls participants according to its own protocol. Participants were evaluated by trained clinicians or interviewers approximately annually at an ADC using a standardized clinical protocol, the Uniform Data Set (UDS). Participant medical and health history is assessed, and participants receive physical and neurologic examinations, plus a battery of neuropsychological assessments. Additional details are available online (alz.washington.edu/WEB/forms_uds.html) and are published elsewhere.^{19,20} Neuropathologic data are collected from neuropathologists on the basis of autopsy results among participants who die and had consented to autopsy evaluation at an ADC.^{21,22}

The current analyses focused on UDS participants who had been autopsied as of September 2018. To focus on the most common types of dementia that occur in community-dwelling older adults,²³ we excluded participants from the primary analysis sample if they had (1) a rare disease ($n = 1,441$ excluded) such as Down syndrome, prion disease, autosomal dominant genetic diseases (i.e., early-onset AD), or frontotemporal lobar degeneration (FTLD) or (2) age at death < 55 years ($n = 128$ excluded). We also excluded participants missing a clinical visit proximal to death (within 2 years; $n = 875$ excluded) so that we would have near-death information on cognitive status and covariates. Participants missing information on hearing abilities, demographics (age, sex, race, education), or common neuropathologies were also excluded ($n = 234$). In total, 2,755 autopsied participants met inclusion criteria for primary analyses. In a secondary analysis, we added participants with FTLDs ($n = 703$) to the analytic sample to examine associations with impaired hearing and FTLD.

Hearing impairment

History of impaired hearing was assessed at each annual UDS visit on the basis of clinician interview (UDS Form B1; type of clinician is not specified for this form and could vary by ADC). Clinicians were asked 3 related hearing questions: (1) Without a hearing aid, is the individual's hearing functionally normal?(yes, no, unknown)? (2) Does the individual usually wear a hearing aid (yes, no, unknown)? (3) If yes, is the individual's hearing functionally normal with a hearing aid? Clinicians filling out the form were instructed to select "no" to questions 1 and 3 if any functional impairment exists (reduced ability to do everyday activities such as listening to the radio or television, talking with family or friends). Answers could be based on report of participant or coparticipant, clinician

judgement, basic clinical examination, or medical history with audiology results.

In the current analysis, we defined impaired hearing according to whether the participant was noted to have impaired hearing at baseline (e.g., not functional hearing in question 1) regardless of hearing aid status. We conducted a subanalysis to evaluate associations with development of hearing impairment over follow-up (e.g., those who had normal hearing reported at baseline but who had hearing impairment reported in a follow-up visit). We also examined hearing aid use defined on the basis of whether the participant was noted to use hearing aids at baseline.

Covariates

NACC UDS forms collect a variety of participant characteristics, medical history, neurologic evaluation, neuropsychological battery, and clinician ratings. We selected a limited set of covariates for the current analyses. Demographic characteristics included age, sex, education, and race/ethnicity. History of health conditions, including vascular risk factors (hypertension and hypercholesterolemia), diabetes mellitus, any cardiovascular disease, and stroke, was recorded at each clinical visit as recent/active, remote/inactive, or absent. Participants were asked whether they had depression in the 2 years before the visit or presence of depressive episodes >2 years before the clinical visit; we defined a history of depression as any recent or remote depressive episodes. We defined a history of each comorbidity (recent or remote) according to the last clinical visit before death. *APOE* genotyping was performed on consenting participants. *APOE* ε4 allele status was classified as at least 1 or none. The Clinical Dementia Rating Dementia Staging Instrument Sum of Boxes (CDR-SB) score,²⁴ a composite measure of the overall level of cognitive impairment and functional disability that is based on clinical judgment and study coparticipant report, was collected at each study visit. Participants also completed a neuropsychological battery of 11 tests.^{25,26} but those with severe dementia often are unable to complete tests, and exact tests changed in 2015, so we focused on the CDR-SB as a measure of overall cognition and dementia staging in the current study because it is available for all participants. Cognitive status was evaluated at each visit, and a diagnosis was made by either a single clinician or a consensus group of clinicians after a review of all evaluation information available, including neuropsychological testing and neurologic examination. Normal cognition (UDS Form D1) was defined as (1) no diagnosis of mild cognitive impairment²⁷ or dementia on the basis of consensus criteria²⁸ and (2) either a CDR score of 0 or neuropsychological testing within normal range (or both). We dichotomized participants on the basis of normal cognition vs cognitively impaired (range from mild impairments to severe dementia).

Neuropathologic features

ADCs follow consensus-based guidelines but conduct neuropathologic assessments according to center-specific

protocols.^{21,22} Neuropathologists used a standardized form, and results were uploaded to the NACC database. AD neuropathologic change (ADNC) included Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores of neuritic plaque densities (none, sparse, moderate, frequent)²⁹ and Braak stages for neurofibrillary tangle pathology (categorized as none, I/II, III/IV, V/VI).³⁰ ADNC was also categorized semiquantitatively (no/low, intermediate, and high). No/low ADNC was defined as no/sparse neuritic plaques and any Braak stage or any neuritic plaques density and Braak stage 0 to II. Intermediate ADNC was defined as moderate or frequent CERAD plaques and Braak stage III to IV, and high ADNC was defined as moderate or frequent plaques and Braak stage V to VI. This assessment does not include Thal phasing³¹ for amyloid plaques, so this operationalization overlaps with but does not correspond exactly to the levels of ADNC as defined by the National Institute on Aging–Alzheimer's Association criteria.³² PART was classified as present in participants with definite PART as defined by Braak stage I to IV and no neuritic plaques in the absence of consistent Thal phase assessments historically.³³ Cerebrovascular pathology encompassed VBI and indicators of vessel disease. In all samples, VBI was defined as any gross infarcts or cortical microinfarcts. In NACC, gross infarcts (present, absent) were defined as large artery or lacunar infarcts identified macroscopically regardless of age. Cortical microinfarcts (present, absent) were defined as infarcts in the cortex that were detected only microscopically. Overall severity of cerebral amyloid angiopathy (identified with stains for amyloid) and atherosclerosis (identified grossly) was recorded as none, mild, moderate, or severe. Presence of Lewy bodies was assessed according to established guidelines and classified as none, brainstem predominant, limbic (transitional), neocortical (diffuse), or region not specified/other.³⁴ Hippocampal sclerosis was classified as present or absent. Presence of FTLN subtypes was documented. For this analysis, we categorized FTLN into tau-positive subtypes (FTLN-tau; e.g., Pick disease, corticobasal degeneration, progressive supranuclear palsy, and other tauopathies) and nontauopathy FTLN subtypes (e.g., FTLN with TAR DNA-binding protein 43 [TDP-43], ubiquitin-positive/tau-negative inclusions, no distinctive histology, or not specified but not a tauopathy). Assessment of TDP-43 was not questioned on the NACC neuropathology forms until 2014.

Statistical analyses

Participant characteristics were described for those with and without hearing impairment. As indirect evidence of the validity of our measure of impaired hearing, we evaluated whether the measure corresponded with well-established epidemiologic patterns in age-related hearing impairment,³⁵ i.e., that the prevalence of impaired hearing increased with age and was higher for men. We plotted sex-stratified predicted age curves of the prevalence of impaired hearing on the basis of logistic regression with natural cubic splines for age. Multivariable logistic regression models assessed associations between impaired hearing and neuropathologic burden,

focusing on the most common neuropathologic features in NACC: neuritic plaques, Braak stage, neocortical Lewy bodies, gross infarcts, and microinfarcts. We fitted models stratified on baseline cognitive status (normal and cognitively impaired) to compare associations by disease stage. Primary models included adjustment for demographics (age at death, sex, race, education) and months between last visit and death, follow-up time, and ADC. Because late-life health conditions may represent shared risk factors or potential mediators of the relationship between hearing impairment and dementia, we ran a secondary model with additional adjustment for *APOE* ϵ 4 allele and history of the following comorbid conditions: hypertension, hypercholesterolemia, diabetes mellitus, smoking, atrial fibrillation, heart attack, congestive heart failure, depression, and CDR-SB score at the last visit. Odds ratios are commonly interpreted as relative risks (RRs), but odds ratios overestimate the RR for common outcomes such as impaired hearing; we therefore estimated RRs using marginal standardization based on predicted probabilities from logistic regressions in the total sample.³⁶

We ran several sensitivity analyses of the primary models to identify and account for potential biases in the sample to further generalize results. We reran models with hearing aid use as the outcome. Next, we used stabilized inverse probability weights^{37,38} to account for potential sample selection bias and to refer study findings to the overall NACC sample. Weights for autopsy selection and missing hearing measurement were calculated as predicted probabilities according to separate logistic regressions with age, birth year, education, sex, race, *APOE* genotyping conducted, CDR-SB score at the last visit, ADC, and interactions between age and education, sex, race, and CDR-SB score at the last visit as primary predictors; weights for each model were multiplied together. The 95% confidence intervals (CIs) for weighted models were derived from 1,000 bootstrap replications.³⁹ Finally, because criteria for pathologies became more standardized in NACC forms after 2014, we reran analyses in those who had died after 2014.

We also ran several secondary analyses. First, we further examined the association between impaired hearing and diagnostic categories of AD neuropathologic features and PART because both are defined by neuritic plaque and Braak staging. We evaluated the association between impaired hearing and ADNC (low ADNC not PART, intermediate ADNC, high ADNC), PART, and the *APOE* ϵ 4 allele as primary predictors. This analysis focused on those who were cognitively normal at baseline. Next, we evaluated whether the development of impaired hearing over follow-up was associated with any particular neuropathologies as a clue as to whether impaired hearing could be an emerging symptom of dementia-related pathology. This secondary analysis was limited to people with cognitive impairment at baseline who did not have impaired hearing at their first ADC visit. Finally, we evaluated the association between impaired hearing and FTLD subtypes (taupathy and nontaupathy) by adding

704 participants with FTLD to the study sample ($n = 2,755$). Because of the small numbers of participants with FTLD without dementia, we did not stratify by baseline cognitive status. All secondary models were adjusted for age at death, sex, non-White race, education, months between last visit and death, follow-up time, and ADC.

We report 95% CIs, and all tests were 2 sided with $\alpha = 0.05$. Analyses were conducted with R (version 3.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Data availability

Data maintained by NACC are publicly available to researchers by request: alz.washington.edu/WEB/researcher_home.html.

Results

Participant characteristics

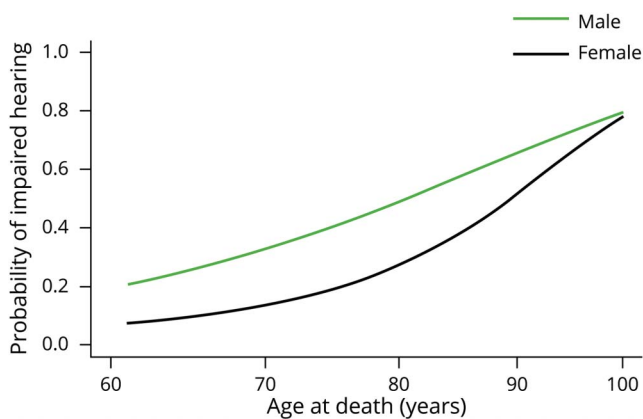
Participants ($n = 2,755$) were followed up for an average of 4.4 years (SD 2.8 years, range 0–12 years) before death. Impaired hearing was common at baseline (32%), and 22% reported hearing aid use (68% of those with impaired hearing). Impaired hearing increased exponentially with age at death and was higher in men (figure 1). Twenty two percent of participants without impaired hearing at baseline developed impaired hearing at a follow-up visit. Table 1 shows participant characteristics by baseline hearing impairment status. Participants with impaired hearing at baseline were on average less likely to be female, to have cognitive impairment, and to carry an *APOE* ϵ 4 allele. They were on average older and more likely to have heart disease, stroke, and hypertension. ADNC and Lewy body disease were less common in those with impaired hearing, but PART and gross or microscopic infarcts were more common in those with impaired hearing (table 1).

Hearing impairment and neuropathologies in participants cognitively normal at baseline

There were 580 participants with normal cognition at baseline (the time of hearing reporting), among whom 37.6% had impaired hearing. One hundred ninety-eight participants were seen multiple times; those with impaired hearing at baseline were slightly more likely to become cognitively impaired by the last visit compared to those without impaired hearing (55% vs 45%).

Table 2 shows the association between impaired hearing and common neuropathologies. In models adjusted for demographics, impaired hearing at baseline was associated with higher Braak stage: participants were 1.33 times more likely to have impaired hearing per increase in Braak stage (operationalized as 0, I/II, III/IV, V/VI) (95% CI 1.06–1.66; table 2). There was a trend toward an inverse association with neuritic plaque density (RR 0.91, 95% CI 0.82–1.01). Neocortical Lewy bodies, gross infarcts, and microinfarcts were not associated with impaired hearing (all $p > 0.05$; table 2).

Figure 1 Prevalence of impaired hearing by age at death



Additional adjustment for *APOE* $\epsilon 4$ allele and health conditions did not substantially change estimates but reduced the sample sizes (table 2).

Estimates were also similar under sensitivity analyses when we included weighting to account for potential selection bias, in models with hearing aid use as the outcome, and in those restricted to autopsies since 2014, but estimates were less precise, and all CIs were consistent with the null (data not shown).

Hearing impairment, ADNC, and PART in participants cognitively normal at baseline

In a separate model, we further examined the link between hearing impairment and the continuum of AD neuropathologic features and PART diagnostic categories (table 3). Impaired hearing was more common in those with high ADNC (RR 1.49, 95% CI 1.15–1.94) and PART (RR 1.32, 95% CI 1.06–1.66) compared to those with low ADNC and not PART. There was a trend toward an inverse relationship with *APOE* $\epsilon 4$ allele (RR 0.85, 95% CI 0.65–1.10).

Because trends seemed to be driven by association with Braak stage, we also plotted the prevalence of impaired hearing by Braak stage (figure 2, which was higher for each increased stage from Braak 0 to V; figure 2). This trend did not differ between those with and those without any neuritic plaques, so results were not stratified.

Hearing impairment and neuropathologies in participants cognitively impaired at baseline

There were 2,175 participants with cognitive impairment at baseline. Table 4 shows the association between impaired hearing and common neuropathologies in participants with cognitive impairment at baseline. In adjusted models, microinfarcts were associated with 1.18-higher likelihood of impaired hearing (95% CI 1.00–1.39; table 4). Neuritic plaques were inversely associated with impaired hearing (RR 0.91 per increase in score, 95% CI

Table 1 Clinical and pathologic characteristics of participants evaluated at NACCs with and without hearing impairment reported at baseline

	Normal hearing (n = 1887), n (%)	Impaired hearing (n = 868), n (%)
Clinical characteristics^a		
Age, mean (SD), y	79.9 (9.5)	86.1 (8.7)
College education	1,076 (57)	503 (57.9)
Female	898 (47.6)	328 (37.8)
Non-White	134 (7.1)	39 (4.5)
≥ 1 <i>APOE</i> $\epsilon 4$ allele	847 (50.0)	319 (41.2)
Baseline cognitive impairment	1,238 (82.1)	917 (71.2)
Depression history	715 (56.0)	557 (53.8)
Hypertension	839 (56.0)	813 (63.4)
Diabetes mellitus	188 (12.5)	154 (12.0)
Ever smoked	606 (47.8)	518 (49.9)
Any heart disease	558 (37.2)	681 (52.9)
Stroke	148 (9.9)	176 (13.7)
Pathologic characteristics		
Frequent neuritic plaques	866 (57.5)	496 (38.5)
Braak stage V/VI	947 (62.8)	620 (48.1)
PART	148 (9.8)	213 (16.5)
Neocortical Lewy bodies	232 (15.4)	173 (13.4)
Gross infarcts	307 (20.4)	312 (24.2)
Cortical microinfarcts	215 (14.3)	231 (17.9)
Severe cerebral amyloid angiopathy	185 (12.6)	152 (12)
Severe atherosclerosis	169 (11.3)	162 (12.7)
Severe arteriolosclerosis	168 (12.7)	147 (12.8)
Hippocampal sclerosis	126 (8.5)	121 (9.5)

Abbreviations: NACC = National Alzheimer's Coordinating Center; PART = primary age-related tauopathy.

^aMissing data: *APOE* genotype 192 (10.0%), depression 228 (11.9%), hypertension 8 (0.4%), diabetes mellitus 2 (0.1%), smoking 242 (12.6%), heart disease 5 (0.3%), stroke 8 (0.4%), cerebral amyloid angiopathy 42 (2.2%), atherosclerosis 18 (0.9%), and arteriolosclerosis 234 (12.2%).

0.85–0.99). Impaired hearing was not associated with Braak stage, neocortical Lewy bodies, or gross infarcts (all $p > 0.05$; table 4). Additional adjustment for *APOE* $\epsilon 4$

Table 2 Association between neuropathologic features and impaired hearing among those with normal cognition at baseline

	Model 1 ^a (n = 580)		Model 2 ^b (n = 444)	
	RR	95% CI	RR	95% CI
Neuritic plaque score	0.91	0.82–1.01	0.90	0.81–1.01
Braak stage	1.33	1.06–1.66	1.29	1.00–1.67
Neocortical Lewy bodies	0.71	0.30–1.67	0.83	0.37–1.90
Gross infarcts	1.01	0.80–1.27	0.98	0.76–1.26
Microinfarcts	0.89	0.66–1.19	0.83	0.61–1.15

Abbreviations: CI = confidence interval; RR = relative risk.
^a Adjusted for age at death, sex, non-White race, education, months between the last visit and death, follow-up time, and Alzheimer's Disease Center.
^b Model 1 + APOE ε4 allele and history of the following comorbid conditions: hypertension, hypercholesterolemia, diabetes mellitus, smoking, atrial fibrillation, heart attack, congestive heart failure, depression, and Clinical Dementia Rating Sum of Boxes score at the last visit.

allele and health conditions did not substantially change estimates but reduced the sample sizes (table 4). We next examined associations with development of impaired hearing; among people who did not have impaired hearing at their first ADC visit, neocortical Lewy bodies (but not other pathologies) were associated with impaired hearing developed after baseline (RR 1.26, 95% CI 1.02–1.55).

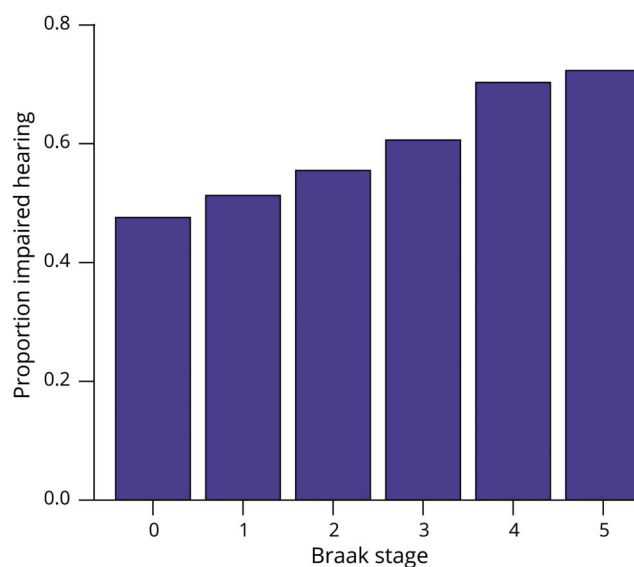
Estimates and overall findings were similar in models with hearing aid use as the outcome. Estimates were also similar under sensitivity analyses when we included weighting to account for potential selection bias and in those restricted to autopsies since 2014, but they were less precise, and all CIs were consistent with the null (data not shown).

Table 3 Associations between impaired hearing and ADNC and PART in those with normal cognition at baseline (n = 580)

	RR ^a	95% CI
APOE ε4 allele	0.85	0.65–1.10
Sparse plaques + Braak stage 0–VI (low ADNC, no PART)	—	—
Moderate/frequent plaques + Braak stage III/IV (intermediate ADNC)	1.14	0.85–1.54
Moderate/frequent plaques + Braak stage V/VI (high ADNC)	1.49	1.15–1.94
No plaques + Braak stage I–IV (PART)	1.32	1.06–1.66

Abbreviations: ADNC = Alzheimer disease neuropathologic changes; CI = confidence interval; PART = primary age-related tauopathy; RR = relative risk.
^a Model adjusted for age at death, sex, non-White race, education, months between last visit and death, follow-up time, and Alzheimer's Disease Center.

Figure 2 Prevalence of impaired hearing increases by Braak stage in participants with normal baseline cognition (n = 545)



Only Braak stages 0 to V are shown because there were few participants with Braak stage VI (n = 35).

Hearing impairment and FTLDs

There were 704 participants with FTLDs; 415 had FTLT-tau, 247 had nontauopathy FTLT, and 41 had both tau and nontau inclusions. In a secondary analysis, we added these 704 participants to the 2,755 participants included in the above analyses and examined the association of impaired hearing at baseline with FTLT subtype with adjustment for age at death, sex, non-White race, education, months between the last visit and death, follow-up time, and ADC. Impaired hearing at baseline was ≈20% less likely in FTLT-tau (RR 0.81, 95% CI

Table 4 Association between neuropathologic features and impaired hearing among those with cognitive impairment at baseline

	Model 1 ^a (2,175)		Model 2 ^b (1,537)	
	RR	95% CI	RR	95% CI
Neuritic plaque score	0.91	0.85–0.99	0.94	0.85–1.04
Braak stage	1.01	0.90–1.13	1.10	0.94–1.28
Neocortical Lewy bodies	1.00	0.85–1.18	1.00	0.82–1.23
Gross infarcts	1.00	0.86–1.18	1.01	0.83–1.22
Microinfarcts	1.18	1.00–1.39	1.20	0.99–1.46

Abbreviations: CI = confidence interval; RR = relative risk.
^a Adjusted for age at death, sex, non-White race, education, months between the last visit and death, follow-up time, and Alzheimer's Disease Center.
^b Model 1 + APOE ε4 allele and history of the following comorbid conditions: hypertension, hypercholesterolemia, diabetes mellitus, smoking, atrial fibrillation, heart attack, congestive heart failure, depression, and Clinical Dementia Rating Sum of Boxes score at the last visit.

0.68–0.96). There was no association between nontauopathy FTLT and impaired hearing (RR 1.04, 95% CI 0.85–1.27).

Discussion

We evaluated the association between clinician-reported impaired hearing and common neuropathologies of aging among older adults evaluated at ADCs. We also examined neuropathologic profiles associated with hearing impairment across stages of cognitive impairment. We found a positive association with higher Braak stage (tau neurofibrillary degeneration) in those with normal cognition at baseline. When considering the ADNC continuum and diagnostic categories, we found that impaired hearing was associated with both high ADNC and PART. In those with cognitive impairment at baseline, there was a positive association with microinfarcts but an inverse association with neuritic plaques (amyloid). Neocortical Lewy bodies were associated with development of hearing impairment over follow-up. We did not find an association between impaired hearing and gross infarcts. In a secondary analysis, FTLT-tau was inversely associated with impaired hearing; however, there was no association between nontauopathy FTLT and impaired hearing. Estimates in sensitivity analyses were generally similar to primary findings, but CIs were wider. Together, these results suggest that reported hearing impairment before dementia onset may be associated with neurofibrillary degeneration related to aging and AD. Hearing impairment later in the clinical disease course may be more strongly associated with other pathologies such as neocortical Lewy bodies and microinfarcts; however, future replication will be needed in studies using biomarkers, objective measures of hearing loss, and population-based samples.

Our finding of an association between impaired hearing (measured before cognitive impairment) and higher Braak stage adds to the literature supporting a biological link of functional hearing impairment before the onset of cognitive impairment with underlying dementia neuropathologies. Prior studies have found associations between hearing loss and future risk of dementia.^{1–6} However, imaging studies focusing on hearing loss (with audiometric tests for peripheral hearing) have produced mixed findings. Some find decreased whole-brain volumes, reduced temporal lobe or auditory cortex volumes,^{16,17} or reduced hippocampal volume.¹⁸ Other studies have found no association between hearing loss and brain volumes.⁴⁰ Animal studies have found that noise-induced (peripheral) hearing loss is associated with increased neurodegeneration in the hippocampus, decreased neurogenesis, and poor memory function.^{41,42} Our finding of an association between clinician-rated hearing impairment before dementia onset and higher neurofibrillary tangles does not establish the direction or causality of the relationship but is consistent with a link between hearing impairment and hippocampal and temporal lobe neurodegeneration.

Clinical judgment of hearing impairment in this study focuses on functional hearing abilities (e.g., hearing radio or conversation) and could encompass deficits in peripheral or central auditory processing,^{7,8} which further adds to the difficulty of inferring causality. Peripheral hearing loss, in particular, may increase cognitive demands or lead to social isolation, which in turn may lead to neurodegeneration.^{9,10} Dementia-related neurodegeneration can affect the central auditory pathways, and thus, we may be capturing effects due to AD or PART that are independent of peripheral hearing loss.¹⁰ Central auditory processing dysfunction, in particular, affects functional hearing such as speech in noise and is thought to be an indicator of preclinical or early AD.^{8,11} However, central auditory dysfunction is difficult to tease apart from cognitive function,^{8,11} and studies in those without cognitive impairment are limited and have focused on specific tests for auditory processing.⁴³ Some studies question a biological link between hearing and cognition; many cognitive tests rely on hearing, and poor hearing may lead to more errors in hearing-based cognitive tests.^{13,14} However, if measurement error were the only explanation for an association, we would expect to find consistent inverse associations between hearing impairment and neuropathologies. Regardless of the mechanism, our findings suggest that clinician-reported impaired hearing may be a preclinical indicator for underlying neurofibrillary pathology. Future studies with biomarkers and objective measures of peripheral hearing and central auditory processing will be needed to establish temporal order and causal mechanisms. Our findings of an inverse association with FTLT-tauopathy suggest that the association between impaired hearing and Braak stage is not related to tauopathy in general but rather neurofibrillary degeneration seen in AD and aging (PART). Studies to examine the distribution of neurofibrillary degeneration within brain regions and other tauopathies could also help better tease apart these relationships.

This study provides a comparison of pathologies associated with hearing impairment before the onset of cognitive impairment and in those with existing cognitive impairment. Difficulty hearing is often reported in patients with AD,⁴⁴ and neurodegeneration in AD affects anatomic structures, including the auditory pathways: neuritic plaques and tangles have been found in auditory association cortex and subcortical auditory pathways, which include the medial temporal lobe.^{45,46} However, these prior studies were small and had no comparison groups.⁴⁷ Unexpectedly, we found a trend toward an inverse association with amyloid plaques in this sample, particularly among those with cognitive impairment at baseline. This inverse association in our study may have resulted because the *APOE* $\epsilon 4$ allele tended to be less common in those with hearing impairment, as has been found in population-based studies.⁴⁸ It is unclear whether this is due to a biological mechanism or survival bias. Participants with cognitive and hearing impairment tended to live to older ages than those with the *APOE* $\epsilon 4$ allele. Alternatively, dementia may affect accuracy or missingness of

our hearing measure, or those with hearing impairment and dementia may be more likely to drop out of ADCs; if this was the case, we may have underestimated the associations between pathologies and hearing impairment in those with dementia. The inverse association with amyloid plaques was weaker (and not significant) in those with normal cognition at baseline; those with high ADNC and PART were more likely to have impaired hearing. The presence of neocortical Lewy bodies was associated with the development of impaired hearing in many of our analyses, particularly in those analyses focused on participants with cognitive impairment and the development of hearing impairment after baseline. Patients with dementia with Lewy bodies often have auditory hallucinations suggesting involvement of the auditory cortex, which may also affect functional hearing abilities.³⁴

VBI (gross or microscopic infarcts) was also more prevalent in older ages, and cortical microinfarcts were more common in those with impaired hearing and dementia. We found an association between cortical microinfarcts and hearing impairment in those with cognitive impairment. Microinfarcts are microscopic infarcts, are often distributed widely⁴⁹ throughout brain regions, and are strongly associated with dementia and cognitive decline in multiple domains.^{50,51} Thus, it is possible that auditory regions are also affected. Vascular disease may contribute to both hearing loss^{52,53} and microinfarct development⁴⁹; however, there was no association between VBI and impaired hearing in those without dementia at baseline. We may have had limited power to detect an association because the severity or burden of infarcts was not collected in a standard way until 2014. Alternatively, this finding may be due to chance. Future work is needed to confirm these associations in other settings.

Our study has a number of limitations. US ADCs, which contribute to NACC, follow up samples that differ from a broader population, mostly comprising White older adults with relatively high socioeconomic status and high risk for clinical AD. In addition, those in the autopsy sample tended to have severe dementia by the last visit. Neuropathologic assessments may not reflect burden of pathology when hearing impairment was reported, although neurodegenerative pathologies begin accumulating decades before symptom onset.^{54,55} We did not have objective audiometric data or separate peripheral and central hearing measurements. Some participants' hearing abilities may have been misclassified. We also did not have information on type of hearing loss, so some participants with genetic or congenital hearing loss may have been included; however, we saw a strong association of the impaired hearing measure with older age. Those with severe cognitive impairment were more likely to have missing data and were not rated as having impaired hearing at baseline as would otherwise be expected. This suggests that our findings may underestimate the magnitude of the

association between hearing impairment and neuropathologies. Despite these concerns, the NACC database represents one of the world's largest and highest-quality multicenter databases, with both detailed clinical and pathologic information. The database has been extensively audited. In addition, we conducted additional secondary and sensitivity analyses to inform the generalizability of our results and potential for selection bias.

Even with the important limitations of our measurements and study sample, this study provides intriguing preliminary evidence that brain pathologies are associated with hearing impairment in a large autopsy sample. We found that impaired hearing before the onset of cognitive impairment was associated with increased neurofibrillary tangles both in AD and in PART. This association was independent of neuritic plaques, which tended to be less frequent in those with hearing impairment, suggesting an association of pathologic neuronal tau and impaired hearing that is independent of β -amyloid. We saw an inverse association, however, with FTLT-tau. Future studies evaluating other tauopathies such as chronic traumatic encephalopathy and aging-related tau astrogliopathy may be informative. Microinfarcts and neocortical Lewy bodies were associated with hearing impairment after the onset of cognitive impairment. Together, these findings are consistent with the hypotheses that hearing impairment may affect brain atrophy and neuropathologic burden or that underlying pathologies may impair functional hearing abilities even before dementia onset. Future studies with biomarker and audiometric information are needed to establish the causal direction of these associations and to verify these findings with objective measures of hearing impairment and in more diverse study populations.

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Disclosure

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Lilah M. Besser, PhD, MSPH	Florida Atlantic University, Boca Raton	Interpreted the data; revised the manuscript for intellectual content
Walter A. Kukull, PhD	University of Washington, Seattle	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
C. Dirk Keene, MD, PhD	University of Washington, Seattle	Role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
M. Maria Glymour, ScD	University of California, San Francisco	Interpreted the data; revised the manuscript for intellectual content
Kristine Yaffe, MD	University of California, San Francisco	Designed and conceptualized study; interpreted the data; revised the manuscript for intellectual content

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