Hearing loss and microstructural integrity of the brain in a dementia-free population

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Under review

ABSTRACT

Background

Hearing loss has been associated with smaller macro structural brain volumes, which is believed to at least partly explain the association between hearing loss and neurodegenerative disease. However, microstructural changes precede macro structural changes. Therefore, we aimed to assess the association between hearing loss and microstructural integrity of the brain.

Methods

1,086 dementia-free participants (mean age = 75.2 [SD: 4.9], 61.4% female) of the population-based Atherosclerosis Risk in Communities (ARIC) study underwent hearing assessment (2016-2017) and magnetic resonance imaging (MRI) of the brain (2011-2013). Hearing was assessed with pure-tone audiometry. Microstructural integrity (fractional anisotropy (FA) and mean diffusivity (MD)) of multiple brain regions was determined with diffusion tensor imaging (DTI). Multivariable linear regression models were used to investigate the association between hearing loss and microstructural integrity of the lobes, temporal lobe gyri, medial temporal lobe structures and white matter (WM) tracts, adjusting for relevant confounders.

Results

Hearing loss was associated with lower WM microstructural integrity in the temporal lobe (mean difference in standardized FA for moderate/severe hearing loss as compared to normal hearing: -0.19 [95% CI: -0.35, -0.03]; and mean difference in standardized MD for moderate/severe hearing loss as compared to normal hearing: 0.15 [95% CI: 0.01, 0.28]). Hearing loss was associated with lower grey matter (GM) microstructural integrity of the hippocampus, but not the amygdala. Moreover, hearing loss was associated with lower WM microstructural integrity of the limbic tracts and the uncinate fasciculus.

Conclusion

Our results demonstrate that hearing loss is associated with lower WM microstructural integrity in the temporal lobe, the limbic tracts and the uncinate fasciculus and lower GM integrity in the hippocampus, brain regions that are important for different cognitive processes. However, the results should be interpreted with caution as this study is of a cross-sectional design.

BACKGROUND

Recently hearing loss has been identified as a promising modifiable risk factor for dementia.[1] Several hypotheses explaining a potential underlying pathway have been proposed, including the sensory-deprivation hypothesis, describing a direct causal relationship in which hearing loss leads to neuroplastic changes in the brain.[2]

Indeed, hearing loss has been associated with smaller brain tissue volumes.[3,4] However, recent studies in the underlying microstructure of brain tissue showed that with aging, microstructural changes precede gross morphological changes.[5] As such, it has been suggested that microstructural degeneration might be a more sensitive and/or earlier marker of neurodegeneration than macro structural atrophy.[5] Therefore, interest in a potential association between hearing loss and microstructural integrity has increased.

Some studies (mostly cross-sectional and consisting of small sample sizes) have reported associations between hearing loss and lower microstructural integrity in the auditory cortex and white matter (WM) tracts.[6-10] So far, only one population-based study reported associations between lower global and tract-specific WM microstructural integrity and poorer hearing.[11] However, they did not assess microstructural integrity of the temporal lobe, where important areas for auditory processing as well as brain structures most relevant in neurodegenerative disease are located.[12] Moreover, diffusion tensor imaging (DTI) was performed on a 1.5 tesla magnetic resonance imaging (MRI) scanner whereas high(er) field strengths are preferred for relatively small structures,[13] such as the limbic tracts. Importantly, these WM tracts might be of interest in regard to hearing loss as they connect parts of the temporal lobe with other regions of the brain that are involved in cognitive processes.[14] Traditionally, DTI has mainly been used to assess WM microstructure. However, interest in the microstructure of the grey matter (GM) has increased. Specifically, it has been reported that high GM mean diffusivity (MD) in the hippocampus was associated with lower memory performance.[15] To our knowledge, no study has assessed a potential association between hearing loss and GM microstructure.

Against this background, we aimed to elucidate the association between hearing loss and WM microstructural integrity of the lobes (frontal, temporal, parietal, occipital), WM microstructural integrity of the gyri of the temporal lobe (superior, middle, inferior), GM MD of medial temporal lobe structures (hippocampus and amygdala), and the microstructural integrity of WM tracts residing in four groups of WM fibre bundles (association, limbic, commissural, sensorimotor) in a population-based sample of older adults.

METHODS

Setting and study population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing population-based prospective cohort study of 15,792 participants aged 45-64 years at recruitment in 1987-1989 from four US communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota).[16, 17]

In visit 6 (2016 – 2017) assessment of hearing was included in the study protocol and 3,655 participants underwent hearing assessment. Of those 3,655 participants, 1,204 participants underwent magnetic resonance imaging (MRI) of the brain at visit 5 (2011 – 2013). Invitation criteria for a brain MRI-scan are described in detail elsewhere.[17] From this sample we excluded participants with prevalent dementia (N = 10), participants with implausible MRI data (N = 4), and participants with probable cognitive impairment (N = 101) (MMSE score ≤ 23 if participants had an educational level of high-school degree or less, or a MMSE score ≤ 25 when participants had an educational level of some college or more). Additionally, due to low numbers we excluded participants if race was other than black or white, or if non-white from Minneapolis and Washington County (N = 3), resulting in an analytical sample of 1,086 participants. The institutional review boards of all participating institutions approved this study and participants provided written informed consent.

Hearing assessment

Pure tone air conduction audiometry was conducted in a sound-treated booth. Air conduction thresholds were obtained at standard frequencies from 0.5 kHz to 8 kHz by trained technicians using an Interacoustics AD629 audiometer (Interacoustics A/S, Assens, Denmark). For participants with a home visit or who were in a long-term care facility, pure tone audiometry was conducted with a portable audiometer and supra aural headphones (Shoebox Audiometer, Ottawa, Canada), after ensuring that the ambient levels of noise in the room were acceptable for valid testing. All thresholds were measured in decibels (dB) hearing level. For all participants, the threshold levels for the pure-tone speech frequencies of 0.5, 1, 2, and 4 kHz in the better hearing ear were averaged to obtain a pure tone average in accordance with the World Health Organization.[18] We categorized pure tone average according to clinically relevant cut points for hearing impairment: normal hearing: ≤ 25 dB; mild: 26-40 dB; moderate/severe > 40 dB. As few participants had severe hearing loss (N = 35; 3.2%), moderate and severe hearing impairment were combined in one category to maintain sufficient statistical power.

Brain imaging and image processing

At ARIC-NCS identical protocols for 3-T brain magnetic resonance imaging (MRI) were used at each study site. The entire scan protocol is described in detail elsewhere.[17]

The protocol included a 3D T1 weighted scan and an axial fluid-attenuated inversion recovery (FLAIR) sequence for atlas region registration and tissue segmentation. For microstructural imaging of the brain, DTI was used. The DTI scans used the Siemens product echo planar imaging (EPI) pulse sequence and diffusion gradient set, namely a single b = 0 volume followed by 64 b = 1,000 s/mm^2 diffusion directions uniformly spread over the whole sphere. An isotropic 2.7 mm voxel resolution was used, and the echo time (TE) was 87 ms for all scanners.

In post-processing the DTI images were simultaneously corrected for eddy current distortion and volume-to-volume head motion by affinely registering each of the diffusion weighted volumes to the b = 0 volume. EPI sequences are also affected by distortions at changes in magnetic susceptibility, such as for example air/tissue/bone interfaces around the sinuses and ear canals. To correct for these distortions, the diffusion weighted data were nonlinearly registered to the T1-weighted anatomical reference scan using the BrainSuite program,[19] which also produced fractional anisotropy (FA) and mean diffusivity (MD) images in each subject's T1-weighted space after fitting diffusion tensors to the data by way of a weighted least-squares scheme. All FLAIR-to-T1 and DTI-to-T1 registrations were manually examined to catch and correct or remove gross registration failures.[17, 20]

DTI measures of FA and MD were used to assess microstructural integrity of lobar and deep WM regions. MD was used to assess microstructural integrity of the temporal lobe GM areas. There is no preferred direction of water diffusion in the GM, therefore GM FA is near 0 and thus it is to be expected that the true GM FA is below the noise limit of DTI scans. FA is a unit less measure of the directional constraint placed on water molecules by cell membranes. MD is the directionally averaged diffusivity of the water molecules, reported here in mm^2/s. Lower WM microstructural integrity is reflected by lower levels of FA and higher levels of MD. Lower GM microstructural integrity is reflected by a higher MD. An in-house atlas derived from the STAND400 template[21] was used to delineate lobar and deep WM regions. For every participant, tissue segmentations from T1-weighted and FLAIR images were intersected with each WM region.[17] Voxels with a greater than 50% probability of being WM, including WM hyperintensities, were used to calculate global FA and MD. To exclude edge voxels that were primarily cerebrospinal fluid, an upper cut-off of MD < 0.002 mm^2/s was applied.[20] We grouped the atlas regions into four regions of interest: frontal, temporal (combined left and right), parietal and occipital lobes. The combination was done by averaging within each group, weighted by the number of voxels in each WM region, to create WM FA and MD measures per structure. Important to note: the diffusion tensor model assumes a single, homogeneous tissue in each measurement voxel, and as such cannot disambiguate changes in individual tissue components to changes in mixing fraction for voxels containing more than one tissue or fibre bundle. However, when corrected for the macro structural effects that

capture most of the compositional differences, differences in MD do essentially reflect changes in the integrity of the tissue for both WM and GM. Next, the JHU "Eve" atlas was nonlinearly registered to the FA image and used to select 18 different regions - tracts and GM structures - in subject native space.[22] Regions were categorized into GM, sensorimotor fibres, association fibres, limbic fibres and commissural fibres. Region-specific measurements of microstructural integrity were obtained by taking median measures inside each region, with subsequent combination of left and right measures. DTI values, both global and region-specific, were measured using fully automated methods (no readers involved).

Covariates

All time-varying covariates are based on data collected at ARIC visit 5. Demographic covariates (collected at visit 1) included date of birth, sex, race (black – Mississippi, black – North Carolina, white – North Carolina, white – Maryland, white – Minnesota), and education.[16] Intracranial volume, normal-appearing WM volume, GM volume and WM hyperintensity volume were quantified via in-house algorithms.[17, 23] All scans included a sagittal T1-weighted 3D volumetric Magnetization Prepared Gradient Echo pulse sequence and a FLAIR sequence. T1-weighted sequences were used for the quantification of brain volumes, FLAIR sequences were primarily used to detect WM hyperintensities.[23] Self-reported information on current and past cigarette smoking was collected and coded as ever or never smoking. Information on alcohol intake was obtained through self-report and defined as alcohol use yes/no. Body mass index (BMI) was defined as weight divided by height squared (kg/m^2). Blood pressure levels were assessed using a random-zero sphygmomanometer after resting for five minutes. The average of the second and third of three consecutive measurements was used to calculate systolic and diastolic blood pressure levels.[24] Hypertension was considered present if diastolic blood pressure was ≥ 90 mm Hg, systolic blood pressure was ≥ 140 mm Hg, and/or the use of antihypertensive treatment.[16] High density lipoprotein (HDL) – cholesterol was measured enzymatically after precipitation of the apolipoprotein B containing lipoproteins. Low density lipoprotein (LDL) – cholesterol was calculated using the Friedewald formula.[24] Hypercholesterolemia was considered present if total cholesterol was ≥ 6.2 mmol/L and/or the use of lipid-lowering medication. Diabetes was defined as a fasting serum glucose level ≥ 126 mg/dL, a non-fasting serum glucose level ≥ 200 mg/dL, and/or a history of diabetes, insulin therapy or oral hypoglycaemic medication use.[16]

Statistical methods

First, we assessed associations of hearing loss continuously and by degrees of hearing loss (mild and moderate/severe hearing loss as compared to normal hearing)) and lobar WM microstructural integrity (frontal, temporal, parietal, and occipital lobe) using

multivariable linear regression models. In the first model we adjusted for age, sex, race per centre, level of education, intracranial volume, normal-appearing WM volume, and WM hyperintensity volume. In the second model we additionally adjusted for smoking, alcohol intake, BMI, hypertension, hypercholesterolemia and diabetes mellitus. Adding age^2 (to account for potential non-linear effects of age), time between visit 5 and 6, the interaction between hearing loss and age and the interaction between hearing loss and sex did not add significantly to the models and were therefore left out of the final analysis. Second, we performed a similar multivariable linear regression analysis in which we studied the association of hearing loss and WM microstructural integrity of the temporal lobe gyri (superior, medial, inferior). Third, we explored associations between hearing loss and GM microstructural integrity of medial temporal lobe structures (hippocampus and amygdala) with the same multivariable linear regression models, though we adjusted for GM volume instead of WM volume. Fourth, we assessed the association of hearing loss and microstructural integrity of specific WM fibre bundles using the same multivariable linear regression models. Effect estimates did not change between models and we therefore report only the full models. To allow comparison between brain regions, we standardized FA and MD values. IBM SPSS statistics version 25.0 (IBM Corp, Armonk, NY, USA) and RStudio; integrated development environment for R, version 3.5.1 (RStudio, Boston, MA, USA) were used for data handling and statistical analyses. Results were considered statistically significant with a p-value ≤ 0.05 (indicated by *) or a p-value ≤ 0.01 (indicated by **). Tests between hearing loss and WM fibre bundles were additionally adjusted for multiple comparisons of the number of tracts studied using a Sidak correction. The number of independent tests were estimated which resulted in a significance threshold at p ≤ 0.0022 (indicated by ***).

RESULTS

Population characteristics are described in Table 1. Mean age was 75.2 years (standard deviation [SD]: 4.9) with a range of 67.0 – 90.0 years. 667 participants (61.4%) were female. Average hearing threshold was 32.4 dB (SD: 13.4) and 338 participants (31.1%) had normal hearing function (hearing threshold ≤ 25 dB).

Hearing loss was associated with lower WM microstructural integrity in the temporal lobe, but not in the frontal, parietal or occipital lobe (Table 2). Specifically, we found that moderate/severe hearing loss as compared to normal hearing was associated with lower FA in the temporal WM (mean difference in standardized FA: -0.19 [95% CI: -0.35, -0.03]). Moreover, hearing loss per 10 dB increase was associated with an on average 0.04 higher standardized MD (95% CI: 0.00, 0.08) and participants with moderate/severe hearing loss had on average a 0.15 higher standardized MD (95% CI: 0.01, 0.28) in the temporal

Table 1. Population characteristics

	N = 1,086
Age, years (SD)	75.2 (4.9)
Age, range in years	67.0 – 90.0
Female, N (%)	667 (61.4)
Education, N (%)	
Basic	106 (9.8)
Intermediate	415 (38.2)
Advanced	563 (51.8)
Center, N (%)	
Forsyth County, North Carolina	277 (25.5)
Jackson, Mississippi	250 (23.0)
Minneapolis, Minnesota	271 (25.0)
Washington County, Maryland	285 (26.2)
Body mass index, kg/m^2 (SD)	28.8 (5.7)
Smoking, yes N (%)	536 (49.4)
Alcohol use, yes N (%)	559 (51.5)
Hypertension, yes N (%)	786 (72.4)
Hypercholesterolemia, yes N (%)	623 (57.4)
Diabetes, yes N (%)	341 (31.4)
Hearing abilities	
Hearing threshold better hearing ear, dB (SD)	32.4 (13.4)
Degree of hearing loss better hearing ear, N (%)	
Normal hearing (≤ 25 dB)	338 (31.1)
Mild (26-40 dB)	454 (41.8)
Moderate/severe (≥ 40 dB)	294 (27.1)
White matter fractional anisotropy, by region	
Frontal lobe (SD)	0.28 (0.02)
Temporal lobe (SD)	0.29 (0.02)
Parietal lobe (SD)	0.30 (0.02)
Occipital lobe (SD)	0.22 (0.02)
White matter mean diffusivity, by region, 10^{-4} mm^2/s	
Frontal lobe (SD)	8.50 (0.50)
Temporal lobe (SD)	8.80 (0.55)
Parietal lobe (SD)	8.70 (0.56)
Occipital lobe (SD)	8.60 (0.59)

dB: decibel. Values are mean (standard deviation) for continuous variables and number (percentages) for dichotomous variables.

Table 2. The association between hearing loss in the better hearing ear and lobe specific white matter microstructure

	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe
	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
			Fractional anisotropy	
Hearing loss, per 10 dB	0.01 (-0.03, 0.05)	-0.04 (-0.08, 0.01)	0.01 (-0.04, 0.05)	0.04 (-0.01, 0.08)
Degree of hearing loss				
None	*Reference*	*Reference*	*Reference*	*Reference*
Mild	-0.00 (-0.12, 0.12)	-0.13 (-0.26, 0.01)	-0.04 (-0.16, 0.09)	-0.02 (-0.16, 0.11)
Moderate/severe	0.03 (-0.11, 0.17)	-0.19 (-0.35, -0.03)**	-0.00 (-0.15, 0.14)	0.08 (-0.08, 0.23)
			Mean diffusivity	
Hearing loss, per 10 dB	-0.02 (-0.06, 0.02)	0.04 (0.00, 0.08)*	0.01 (-0.03, 0.05)	-0.02 (-0.07, 0.02)
Degree of hearing loss				
None	*Reference*	*Reference*	*Reference*	*Reference*
Mild	-0.01 (-0.13, 0.11)	0.07 (-0.05, 0.18)	0.06 (-0.06, 0.18)	0.00 (-0.12, 0.13)
Moderate/severe	-0.02 (-0.16, 0.12)	0.15 (0.01, 0.28)*	0.07 (-0.07, 0.21)	-0.06 (-0.21, 0.09)

Difference represents the mean difference in standardized fractional anisotropy or mean diffusivity per 10 dB increase in hearing thresholds or the mean difference in standardized fractional anisotropy or mean diffusivity per degree of hearing loss (mild, moderate/severe) as compared to normal hearing. Normal hearing ≤ 25 dB. Mild hearing loss: 26 – 40 dB. Moderate/severe hearing loss: ≥ 40 dB. Adjusted for age, sex, race per centre, level of education, intracranial volume, normal-appearing white matter volume, white matter hyperintensity volume, body mass index, hypertension, hypercholesterolemia, smoking (yes/no), alcohol use (yes/no), and prevalent diabetes mellitus. dB: decibel. CI: confidence interval. Lower white matter microstructural integrity is indicated by lower fractional anisotropy and higher mean diffusivity. * $p \leq 0.05$. ** $p \leq 0.01$.

WM compared to participants with normal hearing (Table 2). Those associations were not driven by a specific gyrus in the temporal lobe as effect estimates of the associations between hearing loss and WM microstructural integrity in the superior, medial and inferior temporal gyrus were all comparable (Figure 1; Supplementary table 1).

Hearing loss appeared to be associated with lower GM microstructural integrity in the hippocampus as reflected in higher levels of GM MD, not in the amygdala (Table 3). Associations between hearing loss and the hippocampus were most prominent for moderate/severe hearing loss as compared to normal hearing (mean difference in standardized GM MD: 0.25 [95% CI: 0.11, 0.39]).

Most prominent associations between hearing loss and WM microstructural integrity of the WM fibre bundles were found for the limbic fibres (Figure 2). Hearing loss per 10 dB increase was associated with lower WM FA in the cingulate gyrus part of cingulum, parahippocampal part of the cingulum, fornix (body and column), and the fornix cres stria terminalis as well as with higher WM MD in the parahippocampal part of the cingulum (Figure 2; Supplementary table 2). Mild and moderate/severe hearing loss as

Table 3. Hearing loss in the better hearing ear and grey matter microstructure of medial temporal lobe structures

	Hippocampus mean diffusivity	Amygdala mean diffusivity
	Difference (95% CI)	Difference (95% CI)
Hearing loss, per 10 dB	0.08 (0.04, 0.12)***	-0.01 (-0.05, 0.04)
Degree of hearing loss		
None	*Reference*	*Reference*
Mild	0.13 (0.01, 0.25)*	-0.02 (-0.16, 0.11)
Moderate/severe	0.25 (0.11, 0.39)***	0.03 (-0.13, 0.19)

Difference represents the mean difference in standardized MD per 10 dB increase in hearing thresholds or the mean difference in standardized mean diffusivity per degree of hearing loss (mild, moderate, severe) as compared to normal hearing. Normal hearing ≤ 25 dB. Mild hearing loss: 26 – 40 dB. Moderate/severe hearing loss: ≥ 40 dB. Adjusted for age, sex, race per centre, level of education, intracranial volume, grey matter volume, body mass index, hypertension, hypercholesterolemia, smoking (yes/no), alcohol use (yes/no), and prevalent diabetes mellitus. Lower grey matter microstructural integrity is indicated by higher mean diffusivity. * $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.

compared to normal hearing were both associated with lower WM FA in all limbic fibre bundles (except for mild hearing loss and the cingulate gyrus). Moreover, mild hearing loss was associated with higher WM MD in the parahippocampal part of the cingulum and moderate/severe hearing loss was associated with higher WM MD in the cingulate gyrus and parahippocampal part of the cingulum (Figure 2; Supplementary table 2). No statistically significant associations were found between hearing loss and WM FA in the association fibres. However, hearing loss (per 10 dB increase and moderate/severe hearing loss as compared to normal hearing) was associated with higher WM MD in the uncinate fasciculus (Figure 3; Supplementary table 3). No clinically relevant associations were found between hearing loss and WM microstructural integrity of the sensorimotor fibres and the commissural fibres (Supplementary tables 4 and 5).

DISCUSSION

We found in a dementia-free population-based sample, that hearing loss was associated with lower WM microstructural integrity in the temporal lobe, independent of macro structural measures, but not in the frontal, parietal or the occipital lobe. The association with temporal microstructure was not driven by a specific temporal lobe gyrus. Interestingly, hearing loss was also associated with higher GM MD in the hippocampus. Moreover, we found that hearing loss was associated with lower WM microstructural integrity in the limbic tracts and in the uncinate fasciculus (part of the association tracts).

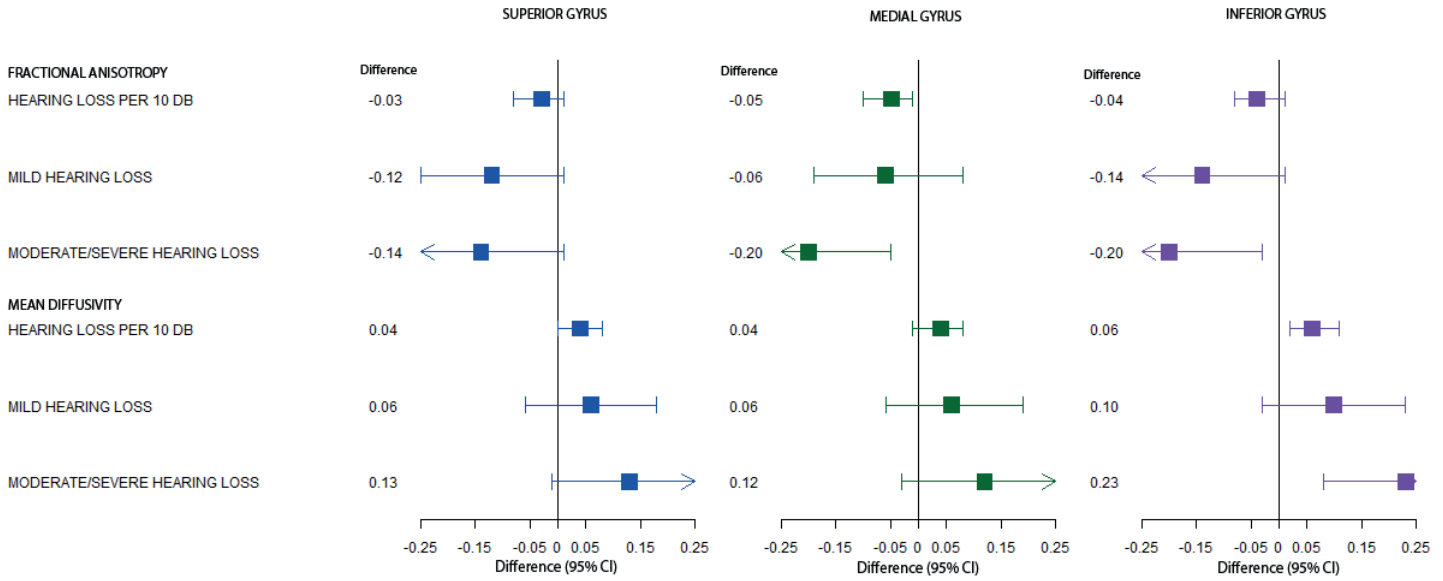

Figure 1. Forest plot of the association between hearing loss in the better hearing ear (per 10 dB increase or mild or moderate/severe hearing loss as compared to normal hearing) and white matter microstructural integrity of the temporal lobe gyri. Difference represents the mean difference (with corresponding 95% CI) of standardized fractional anisotropy or standardized mean diffusivity per 10 dB increase or for mild or moderate/severe hearing loss as compared to normal hearing. Values are adjusted for age, sex, race per centre, level of education, intracranial volume, normal-appearing white matter volume, white matter hyperintensity volume, hypertension, hypercholesterolemia, body mass index, smoking (yes/no), alcohol use (yes/no), and prevalent diabetes mellitus. HL: hearing loss. dB: decibel. SD: standard deviation. CI: confidence interval. Lower white matter microstructural integrity is indicated by lower fractional anisotropy and higher mean diffusivity. For effect estimates with exact 95% CI and statistical significance values, see Supplemental table 1.

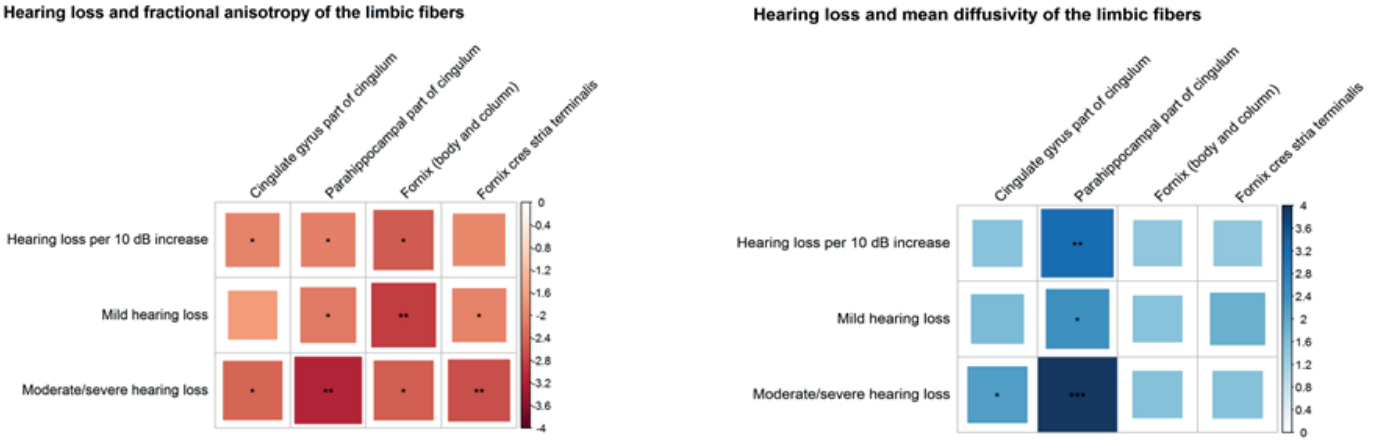

Figure 2. Heat map of the association between hearing loss in the better hearing ear (per 10 dB increase or mild or moderate/severe hearing loss as compared to normal hearing) with white matter microstructural integrity of the limbic tracts reflected by the standardized fractional anisotropy (red; left) and standardized mean diffusivity (blue; right) of the white matter microstructure. Colours and sizes of the blocks correspond to t-values (for effect estimates, see supplemental table 2), with blue and red indicating positive and negative associations, respectively. Values are adjusted for age, sex, race per centre, level of education, intracranial volume, normal-appearing white matter volume, white matter hyperintensity volume, hypertension, hypercholesterolemia, body mass index, smoking (yes/no), alcohol use (yes/no), and prevalent diabetes mellitus. Lower white matter microstructural integrity is indicated by lower fractional anisotropy and higher mean diffusivity. Larger blocks indicate stronger associations, and significance levels as indicated by asterisks: *p ≤ 0·05; **p ≤ 0·01; ***p ≤ 0·0022.

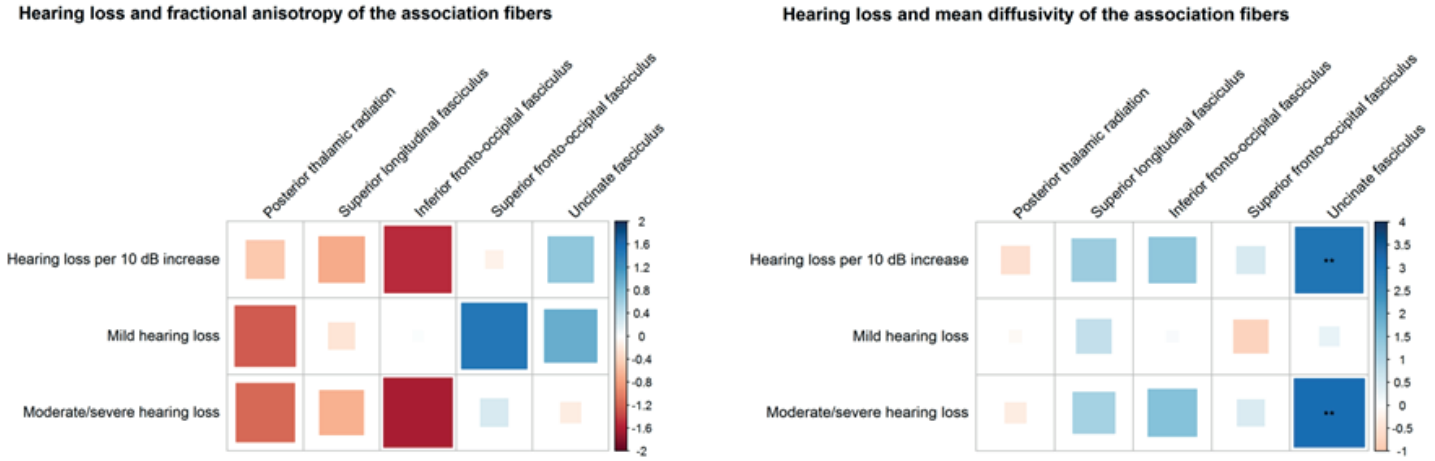

Figure 3. Heat map of the association between hearing loss in the better hearing ear (per 10 dB increase or mild or moderate/severe hearing loss as compared to normal hearing) with white matter microstructural integrity of the association tracts reflected by the standardized fractional anisotropy (red; left) and standardized mean diffusivity (blue; right) of the white matter microstructure. Colours and sizes of the blocks correspond to t-values (for effect estimates, see supplemental table 3), with blue and red indicating positive and negative associations, respectively. Values are adjusted for age, sex, race per centre, level of education, intracranial volume, normal-appearing white matter volume, white matter hyperintensity volume, hypertension, hypercholesterolemia, body mass index, smoking (yes/no), alcohol use (yes/no), and prevalent diabetes mellitus. Lower white matter microstructural integrity is indicated by lower fractional anisotropy and higher mean diffusivity. Larger blocks indicate stronger associations, and significance levels as indicated by asterisks: *p ≤ 0·05; **p ≤ 0·01; ***p ≤ 0·0022.

Strengths of this study include the population-based setting and (quantitative) assessment of microstructural integrity of the brain using diffusion imaging. Moreover, our sample includes a racially diverse population. We also had extensive data on other measurements, enabling us to adjust for potential confounding. In particular, we adjusted analyses for macro structural volumes of relevant brain tissues, so the microstructural differences we found have added value over previously found macro structural changes. Some limitations of the current study should also be acknowledged. First, this is a cross-sectional study, hampering the possibility to infer causality between determinant and outcome. Second, DTI resolution in ARIC is limited in the temporal lobes. EPI distortion is stronger around the inferior surface of the temporal lobe, hampering temporal lobe results. However, if this would have influenced our results, it would have been in the negative direction. Third, as hearing has been measured prior to MRI scanning of the brain, a possible interpretation of our findings is that compromised microstructural integrity leads to hearing loss (i.e., reverse causation). However, there is little (biological) evidence that neurodegeneration precedes hearing loss.[1]

To our knowledge there is only one other population-based study assessing the association between WM microstructural integrity and hearing loss.[3] They reported a whole brain association between lower WM microstructural integrity and higher levels of hearing loss. In contrast, we only found significant associations between increased hearing levels and lower microstructural integrity of the temporal lobe. This contrast may be explained by the fact that the authors of the first study did not consider lobe-specific associations.[3] It is known that the auditory cortex is located in the temporal lobe.[4] Therefore, a whole brain association in the former study may have been driven by associations between hearing loss and the microstructural integrity of the temporal lobe.[3] Indeed, other studies report significant associations between increased levels of hearing loss and microstructural degeneration of the temporal lobe.[5, 6] More specifically, it is known that the auditory regions are located in the superior part of the temporal lobe.[7] Surprisingly, we did not find that associations within the temporal lobe were driven by the superior temporal gyrus. This may point towards a more generalized effect of hearing loss on neurodegeneration of the temporal lobe. However, it may also be an effect of aging in general. The temporal lobe is one of the first areas in the brain to be affected by neurodegeneration with increasing age.[8] Moreover, the current study is of a cross-sectional design, and the mean age is high (75.2 years). Due to this design and the relatively high age of our population we might be unable to adjust for potential residual confounding by age. As such, there is a possibility that our results are partially explained by age-related neurodegeneration, not by hearing loss per se. We tried to circumvent this by adjusting for age[2] in our models as well, but to truly exclude residual effects of aging, longitudinal data are needed.

Interestingly, we found that hearing loss was associated with higher GM MD in the hippocampus. To our knowledge, we are the first study to report this association in humans. A recent study in mice found that hearing loss affected the hippocampus, reflected in altered pre- and post-synaptic markers.[9] Even though our results are promising, care must be taken when interpreting them. The field of diffusion imaging has been growing substantially in the previous years, but mainly in the field of WM microstructural integrity.[10, 11] GM microstructural integrity is a relatively new field in the area of diffusion imaging and up to now it remains unclear what actual accelerated degeneration of the GM microstructure is, apart from 'normal' age-related changes. Interestingly though, it has been found that high GM diffusivity in the hippocampus, before any hippocampal atrophy is visible, is associated with an increased risk for cognitive impairment and dementia.[12] Moreover, another study reported that in dementia-free individuals, higher GM MD was associated with worse performance on memory tasks.[13] However, more longitudinal research is warranted, to establish more in-depth knowledge on GM microstructural degeneration with aging.

Our results did not show an association between hearing loss and GM microstructural integrity of the amygdala. Hearing loss has been associated with depression,[14] for which the amygdala is an important area in the brain.[15] A study from South-Korea found smaller amygdala volumes in patients with hearing loss compared to controls. An absence of an association between hearing loss and the amygdala in our study may be explained by selection bias as people with depressive symptoms may either be less inclined to participate at all in the study or have dropped out of the study at an earlier stage.

In tract-specific WM analyses, significant associations were found between higher levels of hearing loss and lower microstructural integrity of the different tracts located in the limbic fibre bundles and the uncinate fasciculus (part of the association tracts). These results might shed more light on the association between hearing loss and cognitive decline, as the limbic system is a network of cortical and subcortical centres and WM tracts that modulate memory, emotions, and behavior.[16] Moreover, the uncinate fasciculus connects limbic regions in the temporal lobe with areas in the frontal lobe which are involved in behavior.[17] Our results with the uncinate fasciculus are comparable to those of the Rotterdam Study, also reporting associations between lower WM integrity in the uncinate fasciculus and higher levels of hearing loss.[3] However, they did not find associations with the limbic fibre bundles, which is probably explained by different MRI field strengths between studies (1.5 tesla in Rotterdam vs. 3 tesla in the current study) and imaging resolutions, and consequently the limited ability in the Rotterdam Study to track the smaller limbic tracts. Other studies also reported reduced FA values in several WM pathways leading into and out of the auditory cortex. However, those studies consisted of small sample sizes and mostly involved young to middle-aged adults.[6]

Our results may support the sensory-deprivation hypothesis of the effect of hearing on cognition and dementia, as it could be argued that hearing loss has a direct effect on microstructural neurodegeneration of different areas in the brain involved in cognition. However, we should also consider the so-called common-cause hypothesis.[1] This hypothesis states that there is a third factor both causing hearing loss and dementia through central nervous system-wide functional decline, rather than that those two are causally related to one another. As such, greater sensitivity in one domain could identify impairments in that domain prior to the other, leading to the appearance of a false causal relationship.[1] From this view, our results may be explained by a third upstream common cause, rather than that hearing loss is actually related to lower microstructural organization of the brain. To explore whether hearing loss is really related to accelerated neurodegeneration of microstructural organization independent of normal aging effects, longitudinal data are warranted.

To conclude, this study provides new promising evidence pointing towards a direct effect of hearing loss on neurodegeneration as hearing loss appeared to be associated with lower microstructural integrity in the temporal lobe, the hippocampus and the WM tracts of the brain. However, as this study is of a cross-sectional origin we should be cautious with interpreting these results as residual effects of aging on neurodegeneration may still be present. Longitudinal studies in other population-based samples are highly warranted to further elucidate longitudinal associations between hearing loss and potential accelerated degeneration of microstructural integrity of the brain independent of age-effects.

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