White matter microstructure and hearing acuity in older adults: a population-based cross-sectional DTI study

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Neurobiology of Aging 2018

ABSTRACT

To study the relation between the microstructure of white-matter in the brain and hearing function in older adults we carried out a population-based, cross-sectional study. In 2562 participants of the Rotterdam Study, we conducted diffusion tensor imaging to determine the microstructure of the white-matter tracts. We performed pure-tone audiogram and digit-in-noise tests to quantify hearing acuity. Poorer white-matter microstructure, especially in the association tracts, was related to poorer hearing acuity. After differentiating the separate white-matter tracts in the left and right hemisphere, poorer white-matter microstructure in the right superior longitudinal fasciculus and the right uncinate fasciculus remained significantly associated with worse hearing. These associations did not significantly differ between middle-aged (51-69 years old) and older (70-100 years old) participants. Progressing age was thus not found to be an effect modifier. In a voxel-based analysis no voxels in the white matter were significantly associated with hearing impairment.

INTRODUCTION

Progressive sensorineural hearing impairment is a common feature of aging. It is characterized by a gradual decline of hearing thresholds and worse understanding of speech, which seriously affects the quality of life.[1] Although cochlear damage is generally believed to cause age-related hearing impairment, there is strong evidence that age-related hearing impairment also has a central component in its pathogenesis.[2] Moreover, age-related hearing impairment seems to interact with the general cognitive function.[3] Multiple hypotheses on the mechanism between hearing acuity and brain alterations have been outlined. The "common cause hypothesis" describes a mutual factor that affects both hearing acuity as well as brain alterations. This mutual factor could possibly be age, cognition, or an underlying pathological factor such as cardiovascular damage.[4] There are also 2 alternative hypotheses. The "information-degradation hypothesis" describes an indirect effect between hearing and the brain through a shift of cognitive functions. The "sensory-deprivation hypothesis" describes a direct causal relationship in which worse hearing acuity leads to brain alterations.[5] Previous studies using brain imaging have demonstrated that hearing acuity in the aged and middle-aged population relates to morphological brain changes (e.g., gray- or white-matter atrophy.[6,7,8,9] In a previous study in almost 3000 people conducted by our group white-matter atrophy, but not gray-matter atrophy, was associated with age-related hearing impairment.[9] However, apart from the association with gross morphological changes, no conclusion on the underlying white matter microstructure could be made. White-matter microstructure degenerates with aging[10,11] and rates and timing of degradation vary regionally.[12] Reduced organization of white-matter microstructure could repress communication between neurocognitive networks.[13] Previously, auditory and language functions have been ascribed to frontotemporal and parietal white-matter connections[14], especially in the left hemisphere due to functional lateralization. In recent years, diffusion tensor imaging (DTI) has increasingly been used to study brain white-matter tracts. This technique allows for estimation of the microscopic organization of neural tracts by providing information on the diffusion properties of water molecules in the tissue.[15] Parameters that are frequently derived from DTI include fractional anisotropy (FA) and mean diffusivity (MD). Worsening of white-matter integrity is generally reflected in a lower FA and higher MD.[11] The study of Chang et al.was one of the first to investigate the relation between white-matter tracts and hearing function using DTI and pure-tone audiometry.[16] They found a lower FA in the central auditory system in participants with sensorineural hearing impairment. However, they limited their region of interest to the higher auditory system rather than the whole brain. Due to a small sample size, they were not able to correct for confounders. Lin et al. also studied this relation by comparing age-matched participants with hearing impairment

and participants with normal hearing, using DTI and pure-tone audiometry.[17] They also studied the auditory pathway instead of the whole brain and had similar results. Moreover, they found a linear relation between FA and the degree of hearing impairment. Husain et al. conducted a third cross-sectional study and performed DTI on the white matter association tracts.[7] They found a different FA for both hemispheres. The association tracts into and out of the right temporal and frontal cortex had poorer white-matter microstructure in participants with worse hearing thresholds when compared with participants with normal hearing. The same tracts in the left hemisphere were not associated with hearing impairment. These 3 studies have in common that the study samples were small (maximum n = 47), age ranges were wide (between 8 and 85 years old), and authors only focused on specific regions of interest (ROI) in the brain known for their auditory function instead of whole brain analysis. On the contrary, Profant et al. found no significant associations between the organization of white-matter tracts and age-related hearing impairment.[18] They also investigated specific ROIs, and they used an equally small sample size, but they studied relatively old participants (mean age in the older group was 70.4 ± 1.3 years).

Although most of these studies show that microstructural changes in white matter and hearing loss are correlated, some essential issues remain to be investigated.[19] First, ROI's have not consequently been defined, which makes direct comparison of results impossible. It would be useful to additionally study potential changes in brain regions beyond those used for auditory processing. Second, different hearing outcomes have been used (e.g., speech vs. high frequency thresholds) and speech-in-noise ability was not tested. Third, the relationship between cognitive decline, aging, and hearing impairment and their effect on brain structure and function is hard to investigate because of confounding effects. A population-based study could provide an unbiased evaluation of the association between white-matter microstructure and age-related hearing acuity.

To address the above issues, we conducted a large population-based study on community-dwelling older adults. Our primary objective was to analyze the association between the global and tract-specific white-matter microstructure and hearing acuity using DTI. Second, we aimed to investigate the effect of aging on this possible association, because aging is associated with both white matter degeneration and worse hearing acuity. In the analyses, we used both auditory thresholds (low, speech, and high frequencies) and the ability for speech recognition in noise, and we accounted for possible cognitive and cardiovascular covariates. We hypothesized that participants with worse hearing acuity would have a lower FA and higher MD, which corresponds with poorer white-matter microstructure in the tracts. We assumed different outcomes for different tracts, based on anatomy and function, with stronger relations for association tracts directly or indirectly involved in auditory processing such as the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the uncinate

fasciculus. Furthermore, since we hypothesized that aging could amplify the effect between white-matter microstructure and hearing acuity, we expected to find a larger effect in older than in middle-aged participants.

METHODS

Study population

This cross-sectional study is based on participants of the population-based Rotterdam Study, an ongoing prospective cohort study on healthy aging.[20] The Rotterdam Study includes inhabitants of 45 years and older of Ommoord, a Rotterdam district. It currently includes 14,926 participants. Participants undergo several measurements every 3-5 years. From 2005 onward, MRI scanning was added to the study protocol[21] and from 2011 onward, audiometry was incorporated as well. We considered eligible participants with brain MRI, including a diffusion-weighted sequence, and audiometry (N = 2665). We excluded those with cortical infarcts on the scan (N = 61), with dementia (N = 25) or with conductive hearing loss (N = 17), leaving 2562 participants for analysis. Dementia was ascertained as previously described using a 3-step protocol.[22] We excluded 104 participants from the analyses concerning the digits-in-noise (DIN) test. They failed to complete the DIN-test or the result was more than 4 standard deviations from the mean, making results less accurate.[23] The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sports of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

MRI acquisition and processing

Multisequence MRI imaging was performed in a 1.5 Tesla MRI scanner (GE Signa Excite). The MRI protocol included a T1-weighted image (T1w, repetition time 13.8 milliseconds [ms], echo time 2.80 ms, inversion time 400 ms, 96 slices of 1.6 millimeter [mm], matrix 256 x 256), a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (repetition time 8000 ms, echo time 120 ms, inversion time 2000 ms, 64 slices of 2.5 mm, matrix 320 x 224), a proton density-weighted image (repetition time 21,300 ms, echo time 17.3 ms, 90 slices of 1.6 mm, matrix 416 x 256), and a spin echo planar diffusion-weighted image (repetition time 8575 ms, echo time 82.6 ms, 35 slices of 3.5 mm, matrix 64 x 96). Maximum b-value was 1000 s/mm^2 in 25 noncollinear directions. Three volumes were acquired without diffusion weighing (b-value = 0 s/mm^2).[21]

A number of preprocessing steps were performed before analysis.[21] In short, structural scans for each participant were spatially coregistered using rigid registration. After brain masking and nonuniformity correction scans were segmented in gray matter, white matter, cerebrospinal fluid, and background tissue using a supervised approach based on a k-nearest neighbor segmentation approach[24,25] on the T1-weighted and proton density images. Intracranial volume, with the exclusion of the cerebellum and surrounding cerebrospinal fluid, was defined by the sum of gray and white matter and cerebrospinal fluid volumes. The brain tissue segmentation method was followed by a white-matter lesion segmentation. This was performed with an in-house developed automated segmentation method using a 2-step protocol which relies on the brain tissue segmentation and the FLAIR image.[26] We used Elastix[27] to correct the diffusion images for subject motion and eddy currents, using an affine registration. Tensors were estimated using a Levenberg-Marquardt algorithm in ExploreDTI.[28] The same motion corrected diffusion data were also used to estimate the probabilistic model required for ProbTrackx tractography.[29] We performed tractography in native space, using standard space seed, target, stop, and exclusion masks as described previously.[30] The probabilistic tractography algorithm was run with default settings (step length 0.5, curvature threshold 0.2, maximum steps 200). Also, the diffusion model estimation (Bedpostx) was run with default options. Cortical infarcts were visually defined as focal parenchymal lesions <3 mm and >15 mm with involvement of cortical gray matter and with signal characteristics equal to CSF on all sequences and with a hyperintensive rim on the FLAIR image.[31] We computed global mean FA and MD in the normal appearing white matter. FA is the degree of anisotropy and is given as a ratio ranging from 0 (isotropic or non-directional) to 1 (unidirectional). MD is expressed in square millimeters per second. Furthermore, we used the diffusion data to segment 15 (of which 12 segmented bilaterally) white-matter tracts using probabilistic tractography as previously described.[32] Tracts were grouped based on anatomy or presumed functional groups into brainstem tracts (middle cerebellar peduncle and medial lemniscus), projection tracts (corticospinal tract, anterior thalamic radiation, superior thalamic radiation, and posterior thalamic radiation), association tracts (superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinated fasciculus), limbic system tracts (cingulate gyrus part of cingulum, parahippocampal part of cingulum, and fornix), and callosal tracts (forceps major, forceps minor) in the left and right hemisphere.[32] Due to tractography failures or (visually) rejected segmentations, tract-specific measurements were missing for on average 6.9 participants (ranging from 0 to 61 participants) per tract. We obtained tract-specific diffusion measures (mean FA and mean MD per tract.[32] We standardized global and tract-specific diffusion measures (z-scores). We obtained tract-specific white-matter volumes and tract-specific white-matter lesion volumes (natural log-transformed) by

combining tissue and tract segmentations. Varying seed masks were used to account for partial coverage of the medial lemniscus (one of the brainstem tracts), and this was considered as a potential confounder in the analyses in which the medial lemniscus was investigated.

Voxel-based analysis

Voxel-based analysis (VBA) of DTI data was performed according to the voxel-based morphometry method[33] as previously described.[34] FSL software[35] was used for VBA data processing. All FA and MD maps were nonlinearly registered to the standard FA template from the FSL package with a 1 x 1 x 1 mm^3 voxel resolution. In addition, the Rotterdam Study tract template that was used for analyzing the DTI measures per tract was mapped to MNI space, to assess location of association and compare VBA results with global DTI measures. Participant-specific tract segmentation masks[32] were registered to MNI template in the same way as FA and MD maps and then merged to 1 tract template image. We used 90% probability thresholds to define the tract templates.

Audiometry

All audiometry was performed in a soundproof booth by a single qualified health professional. A clinical audiometer (Decos audiology workstation, version 210.2.6, with AudioNigma interface), TDH-39P earphones and B71 bone conductor were used. Pure-tone audiometry thresholds were measured according to the International Organization for Standardization 8253-1 (International Organization for Standardization, 2010). Air conduction (0.25, 0.50, 1, 2, 4, and 8 kHz) and bone conduction (only 2 frequencies due to limited time: 0.5 and 4 kHz) were tested for both the ears. Masking was done according to the method of Hood.[36] Bone conduction thresholds at 4 kHz were compensated with +10 decibel (dB) afterward.[38] We determined the best hearing ear by calculating the average threshold over all frequencies. If both the ears were equal, right or left was alternately chosen. Of the best hearing ear, we then determined the low (average of 0.25, 0.50 and 1 kHz), speech (average of 0.50, 1, 2 and 4 kHz), and high frequency hearing thresholds (average of 2, 4 and 8 kHz). We excluded participants with an air-bone gap of 15 dB or more to eliminate clinically relevant conductive hearing loss. In addition, the DIN-test was performed to detect the speech recognition ability in noise.[39] Again, this was done for the best hearing ear. The test measures a speech reception threshold by letting participants repeat digit triplets in an automated adaptive procedure and changing the signal to noise ratio according to the correctness of the answer. The speech reception threshold represents a speech-in-noise ratio for 50% correctly repeated triplets. A higher value represents a worse ability of understanding speech in noise. To avoid confounding for peripheral hearing acuity, we

additionally adjusted for the high frequency hearing thresholds in the analyses with the DIN-test.
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Other covariates

Information on various covariates was collected through a home interview at enrollment of the study, or by recurrent physical examination and blood sampling at the study center. Education was qualified as having completed primary level, secondary level, or higher education. Mini-Mental State Examination (MMSE) score, body mass index, systolic and diastolic blood pressure, diabetes mellitus, cholesterol ratio, smoking habits, and alcohol consumption were reassessed every follow-up visit. Diabetes mellitus was stated present when fasting glucose was 7 mmol/L or more, or (if unavailable) when nonfasting glucose was 11 mmol/L or more, or when participants used antidiabetics. Cholesterol ratio was calculated via the quotient of serum total-cholesterol and high-density cholesterol. Smoking was categorized as never, former, or current. Alcohol consumption was categorized as non-drinker, light consumer (1 unit of alcohol per day for women and 1-2 units of alcohol per day for men) or above average consumer (more than 1 unit of alcohol per day for women and more than 2 units of alcohol per day for men.[40] We used the data on covariates from the same follow-up round as the MRI and audiometry measurements. Except for the MMSE-score, which was registered 1 round earlier.

Statistical analysis

Associations between DTI measurements (FA and MD) and hearing acuity were explored using multivariable linear regression models. Global and tract-specific FA and MD were regarded as independent variables, and pure-tone thresholds and score on the DIN-test as dependent variables. We calculated regression coefficients and 95% confidence intervals (CIs). Significance was set at $p < 0.05$ for the analyses concerning global DTI measurements. To account for multiple testing in the tract-specific analyses, we used the Sidak-correction, which was set at $p < 0.00248$ for the analyses in which we averaged left and right tract-specific measures and set at $p < 0.00156$ for the tract-specific analyses of left and right separately. To adjust for the covariates, we used 2 models. Model 1 was the 'simple' model and adjusted for age, gender, time between DTI and audiometry, intracranial volume, white-matter volume and white-matter lesions (log-transformed, global, or tract-specific). Model 2 was extended with possible confounders on the association between altered white-matter tracts and hearing acuity. Specifically, we investigated the impact of potential vascular confounders, known for their association with altered white matter[32] and hearing acuity.[1] Model 2 further

adjusted for: education, MMSE-score, body mass index, systolic and diastolic blood pressure, the presence of diabetes mellitus, cholesterol ratio, and smoking and alcohol consumption. For analyses involving the medial lemniscus, we additionally adjusted for the varying position of seeds masks. In the analyses on the DIN-test, we adjusted for high frequency hearing loss as well. We repeated the analyses after stratification between middle-aged (51-69 year old) and older participants (70-100 years old). We examined the presence of multicollinearity and found no variance inflation factor larger than 4. For the VBA linear regression models were fitted with voxel values of FA and MD measures as dependent variables and pure-tone thresholds and score on the DIN-test as independent variables. Furthermore, we corrected the VBA models like the DTI models (mentioned previous). For this analysis, all voxels within the white-matter mask were used. To estimate the threshold for significance, a nonparametric permutation test was performed independently for FA and MD. We shuffled the data randomly 5000 times and performed VBA. For every permutation, we saved the minimum p-value. Subsequently, we took the 5th percentile of this minimum p-value distribution to compute the family-wise error p-value threshold, which was 1.21×10^{-7} for FA and 1.23×10^{-7} for MD.[41] To map the significant voxels to the tract location, we created a tract study-specific atlas. Subject-specific tract segmentations[32] were registered to MNI template using FSL software. All these transformed images were merged and divided by number of participants to make a probabilistic tracts template. Due to between-participants variation in tract location, probabilistic templates allowed us to map voxels with different certainty.

Missing data were minimal (0.4% of total data) and were imputed in SPSS using fivefold multiple imputation with an iterative Markov chain Monte Carlo method, based on determinant, outcome, and included variables. Distribution of covariates was similar in the imputed and the nonimputed data set. We pooled the data by aggregating the file in SPSS before analyzing it in R. Data analysis was performed using IBM SPSS Statistics version 21 (IBM, Armonk, NY, USA), and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The demographic characteristics of the 2562 participants are provided in **Table 1**. Hearing thresholds on the pure-tone audiogram were higher toward the higher frequencies, as typically seen in age-related hearing impairment (**Figure 1**).

Table 1. Demographic characteristics of the study population (N = 2,562).

Characteristic	
Age, years	69.3 ± 9.6
Gender, female	1,412 (55.1%)
Education, primary	176 (6.9%)
Education, secondary	1,762 (68.8%)
Education, higher	597 (23.3%)
MMSE score (median, IQR)	29 (27;29)
Body mass index, kg/m^2	27.3 ± 4.0
Systolic blood pressure, mmHg	144 ± 21.4
Diastolic blood pressure, mmHg	84 ± 11.0
Diabetes mellitus, yes	332 (13.0%)
Cholesterol ratio	3.90 ± 1.21
Smoking, never	863 (33.7%)
Smoking, former	1,323 (51.6%)
Smoking, current	368 (14.4%)
Alcohol, never	354 (13.1%)
Alcohol, light drinker	2,077 (77.9%)
Alcohol, above average	222 (8.7%)
FA, global white matter	0.34 ± 0.016
MD, global white matter (x 10^{-3} mm^2/s)	0.75 ± 0.027
PTA low frequencies, dB	17.2 ± 10.7
PTA speech frequencies, dB	24.8 ± 13.6
PTA high frequencies, dB	37.9 ± 19.5
DIN-score* (median, IQR)	-5.0 (-6.4;-2.4)

dB = Decibel; DIN = Digits-in-noise test; FA = Fractional anisotropy; IQR = Inter quartile range; MD = Mean diffusivity; MMSE = Mini-Mental State Examination; PTA = Pure-tone audiometry.
*For DIN N = 2,408.

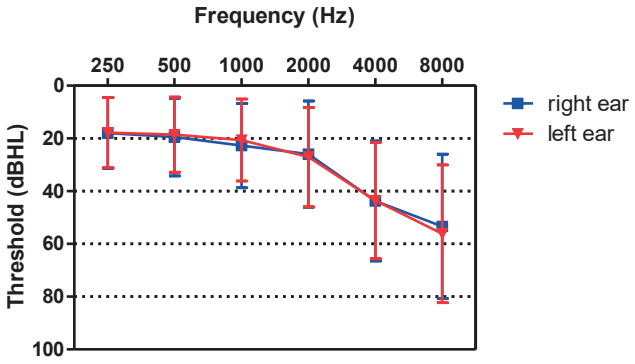

Figure 1. Mean hearing thresholds on the pure-tone audiogram of all participants (N = 2,562). Error bars indicate 95% CI.dBHL = Decibel Hearing Level; Hz = Hertz.

The association between global DTI measures and hearing acuity is presented in **Table 2**. To compare the effect of the DTI measures, the betas of the most important covariates (age, gender, and MMSE-score) are also shown. A lower FA was significantly associated with worse hearing acuity, that is, higher hearing thresholds on the pure-tone audiogram (beta per SD decrease in FA = 0.69 dB, 95% CI 0.24; 1.14) and worse performance on the DIN-test (beta per SD decrease in FA = 0.19 signal to noise ratio, 95% CI 0.05; 0.32). Adjusting for the covariates in model 2 showed stronger associations (beta per SD decrease in FA = 0.86 dB on the pure-tone audiogram, 95% CI 0.41; 1.30 and 0.23 signal to noise ratio on the DIN-test, 95% CI 0.09; 0.37). A higher MD was significantly associated with worse hearing acuity on the pure-tone audiogram for the speech and higher frequencies in model 2. MD and the outcomes of the DIN-test were not significantly associated. Subsequently, we analyzed the association between tract-specific DTI measurements and hearing acuity (**Supplemental Tables 1 and 2**). The association of a lower FA and worse hearing acuity was primarily found in the association tracts: superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (**Table 3**). However, only the association between the superior longitudinal fasciculus and worse hearing on the pure-tone audiogram and the association between the uncinate fasciculus and worse performance on the DIN-test were still significant after the multiple testing correction ($p < 0.0024$).

When differentiating the tracts between left and right hemisphere (**Supplemental Tables 3 and 4**), a lower FA of the right superior longitudinal fasciculus remained significantly ($p < 0.00156$) associated with worse hearing on the pure-tone audiogram. A higher MD of the right uncinate fasciculus was also significantly ($p < 0.00156$) associated with worse hearing on the pure-tone audiogram, whereas the MD of the left and right uncinate fasciculus combined was not (**Supplemental Table 2**). Both significant tracts (superior longitudinal fasciculus and uncinate fasciculus) are displayed by a tractographic reconstruction in **Figure 2** and **Figure 3**. To address our second objective -examining whether there is a different effect caused by progressive aging- we stratified our results into a middle-aged (51-69 years old, n = 1390) and older (70-100 years old, n = 1172) group. The associations between global DTI measurements and pure-tone audiogram were significant in the middle-aged group, but not in the older group. On the other hand, the associations between global DTI measurements and the DIN-test were significant in the older group, but not in the middle-aged group. However, interaction was not significant (**Supplemental Table 5**). Finally, we performed VBA on the white-matter tracts to examine whether specific tract-subregions showed primarily associations with worse hearing acuity. FA and MD in the voxel-based analysis were not associated with hearing acuity on both the pure-tone audiogram and the DIN-test.

Table 2. Association between global DTI measures and hearing acuity.

	PTA (N = 2,562)				DIN (N = 2,408)
	ALL	LOW	SPEECH	HIGH	
↓ in FA (model 1)	**0.69 (0.24; 1.14) 0.002**	**0.42 (0.00; 0.84) 0.049**	**0.72 (0.24; 1.20) 0.003**	**0.97 (0.34; 1.59) 0.002**	**0.19 (0.05; 0.32) 0.008**
↑ in Age, per year	**0.92 (0.86; 0.99) 0.000**	**0.53 (0.47; 0.60) 0.000**	**0.81 (0.74; 0.89) 0.000**	**1.31 (1.21; 1.40) 0.000**	-0.02 (-0.04; 0.00) 0.054
Gender, male	**2.46 (1.51; 3.41) 0.000**	**-1.32 (-2.20;-0.47) 0.003**	**2.29 (1.27; 3.30) 0.000**	**6.25 (4.94; 7.57) 0.000**	**-0.38 (-0.67;-0.08) 0.011**
↓ in FA (model 2)	**0.86 (0.41; 1.30) 0.000**	**0.56 (0.14; 0.97) 0.008**	**0.87 (0.40; 1.36) 0.000**	**1.15 (0.53; 1.78) 0.000**	**0.23 (0.09; 0.37) 0.001**
↑ in Age, per year	**0.90 (0.83; 0.98) 0.000**	**0.51 (0.45; 0.58) 0.000**	**0.80 (0.72; 0.88) 0.000**	**1.30 (1.19; 1.40) 0.000**	-0.02 (-0.04; 0.00) 0.059
Gender, male	**1.97 (0.99; 2.95) 0.000**	**-1.68 (-2.59;-0.77) 0.000**	**1.85 (0.80; 2.90) 0.001**	**5.63 (4.26; 6.99) 0.000**	**-0.39 (-0.70; -0.09) 0.010**
↑ in MMSE, per point	**-0.40 (-0.64;-0.16) 0.001**	**-0.27 (-0.49;-0.04) 0.018**	**-0.33 (-0.59;-0.08) 0.010**	**-0.53 (-0.87;-0.19) 0.002**	**-0.17 (-0.24; -0.09) 0.000**
↑ in MD (model 1)	0.43 (-0.09;0.94) 0.103	0.16 (-0.32;0.63) 0.524	0.41 (-0.14;0.96) 0.140	0.70 (-0.14;0.96) 0.055	0.03 (-0.13;0.18) 0.733
↑ in Age, per year	**0.92 (0.85; 0.99) 0.000**	**0.53 (0.47; 0.60) 0.000**	**0.81 (0.74; 0.89) 0.000**	**1.30 (1.20; 1.40) 0.000**	-0.22 (-0.04; 0.00) 0.075
Gender, male	**2.46 (1.51; 3.41) 0.000**	**-1.33 (-2.22;-0.45) 0.003**	**2.28 (1.26; 3.30) 0.000**	**6.26 (4.94; 7.59) 0.000**	**-0.39 (-0.69; -0.10) 0.008**
↑ in MD (model 2)	**0.58 (0.07; 1.09) 0.026**	0.29 (-0.18;0.77) 0.228	**0.57 (0.02; 1.12) 0.042**	**0.87 (0.15; 1.58) 0.017**	0.07 (-0.09;0.23) 0.377
↑ in Age, per year	**0.90 (0.82; 0.97) 0.000**	**0.51 (0.44; 0.58) 0.000**	**0.80 (0.72; 0.88) 0.000**	**1.29 (1.18; 1.39) 0.000**	-0.02 (-0.04; 0.00) 0.069
Gender, male	**1.99 (1.00; 2.97) 0.000**	**-1.68 (-2.59;-0.76) 0.000**	**1.87 (0.81; 2.92) 0.001**	**5.66 (4.29; 7.03) 0.000**	**-0.40 (-0.71; -0.10) 0.009**
↑ in MMSE, per point	**-0.39 (-0.63;-0.15) 0.001**	**-0.26 (-0.49;-0.04) 0.021**	**-0.33 (-0.59; -0.07) 0.013**	**-0.52 (-0.86;-0.18) 0.002**	**-0.16 (-0.24; -0.09) 0.000**

Outcomes indicate the change in hearing threshold (in decibel) for the PTA and the change in speech reception threshold for the DIN-test per standard deviation change of the DTI measures and most important covariates. Significant findings ($p < 0.05$) are shown in bold and confidence intervals (95%) are shown in brackets.

DIN = Digits-in-noise test; DTI = Diffusion tensor imaging; FA = Fractional anisotropy; MD = Mean diffusivity; MMSE = Mini-Mental State Examination; PTA = Pure-tone audiometry.
All = average threshold 0.25 / 0.50 / 1 / 2 / 4 / 8 kHz, low = average threshold 0.25 / 0.50 / 1 kHz, speech = average threshold 0.50 / 1 / 2 / 4 kHz, high = average threshold 2 / 4 / 8 kHz.
Model 1 is corrected for time between DTI and audiometry, white matter volume (ml), white matter lesion volume (log-transformed), and intracranial volume (ml). Model 2 is corrected as model 1 plus systolic and diastolic blood pressure, body mass index, diabetes mellitus, cholesterol ratio, education, score on the Mini-Mental State Examination, smoking, and alcohol consumption.
In the DIN-analyses high frequency hearing loss was also accounted for.

Table 3. Association between the FA of the association tracts and hearing acuity.

	PTA (N = 2,562)				DIN (N = 2,408)
	ALL	LOW	SPEECH	HIGH	
SLF (model 1)	0.70 (0.20; 1.19) 0.005	0.37 (-0.09; 0.83) 0.114	0.62 (0.09; 1.15) 0.021	1.02 (0.34; 1.71) 0.003	0.00 (-0.15; 0.15) 0.994
SLF (model 2)	**0.84 (0.35; 1.34)*** **0.000**	0.49 (0.03; 0.95) 0.036	0.76 (0.24; 1.29) 0.004	**1.20 (0.52; 1.89)*** **0.000**	0.04 (-0.11; 0.19) 0.571
ILF (model 1)	0.58 (0.11; 1.05) 0.015	0.42 (-0.02; 0.85) 0.060	0.57 (0.07; 1.07) 0.026	0.74 (0.09; 0.74) 0.026	0.08 (-0.07; 0.22) 0.287
ILF (model 2)	0.62 (0.16; 1.09) 0.008	0.46 (0.03; 0.89) 0.037	0.62 (0.12; 1.12) 0.015	0.79 (0.14; 1.44) 0.017	0.10 (-0.05; 0.24) 0.182
IFO (model 1)	0.59 (0.10; 1.08) 0.018	0.43 (-0.03; 0.89) 0.066	0.65 (0.12; 1.17) 0.016	0.75 (0.07; 1.44) 0.031	0.13 (-0.03; 0.28) 0.102
IFO (model 2)	0.67 (0.18; 1.16) 0.007	0.50 (0.04; 0.95) 0.033	0.73 (0.20; 1.25) 0.006	0.84 (0.16; 1.53) 0.015	0.15 (0.00; 0.30) 0.049
UNC (model 1)	0.28 (-0.21; 0.77) 0.257	0.19 (-0.26; 0.65) 0.405	0.34 (-0.19; 0.86) 0.208	0.37 (-0.31; 1.05) 0.283	0.19 (0.04; 0.34) 0.011
UNC (model 2)	0.41 (-0.08; 0.90) 0.097	0.30 (-0.16; 0.75) 0.198	0.46 (-0.06; 0.98) 0.084	0.52 (-0.15; 1.20) 0.128	**0.23 (0.08; 0.38)*** **0.002**

Outcomes indicate the change in hearing threshold (in decibel) for the PTA and the change in speech reception threshold for the DIN-test per standard deviation decrease of FA. Significant results ($\alpha < 0.05$) are shown in normal font, results that survived multiple testing ($p < 0.00156$) are shown in bold and with *. Confidence intervals (95%) are shown in brackets.

DIN = Digits-in-noise test; DTI = Diffusion tensor imaging; FA = Fractional anisotropy; IFO = Inferior fronto-occipital fasciculus; ILF = Inferior longitudinal fasciculus; PTA = Pure-tone audiometry; SLF = Superior longitudinal fasciculus; UNC = Uncinate fasciculus.
All = average threshold 0.25 / 0.50 / 1 / 2 / 4 / 8 kHz, low = average threshold 0.25 / 0.50 / 1 kHz, speech = average threshold 0.50 / 1 / 2 / 4 kHz, high = average threshold 2 / 4 / 8 kHz.
Model 1 is corrected for age, sex, time between DTI and audiometry, white matter volume, white matter lesions volume (log-transformed), and intracranial volume (ml). Model 2 is corrected as model 1 plus systolic and diastolic blood pressure, body mass index, diabetes mellitus, cholesterol ratio, education, score on Mini-Mental State Examination, smoking, and alcohol consumption.
In the DIN-analyses high frequency hearing loss was also accounted for.

To address our second objective – examining whether there is a different effect caused by progressive aging– we stratified our results into a middle-aged (51-69 years old, n = 1,390) and older (70-100 years old, n = 1,172) group. The associations between global DTI measurements and pure-tone audiogram were significant in the middle-aged group, but not in the older group. On the other hand, the associations between global DTI measurements and the DIN-test were significant in the older group, but not in the middle-aged group. However, interaction was not significant (**Supplemental Table 5**).

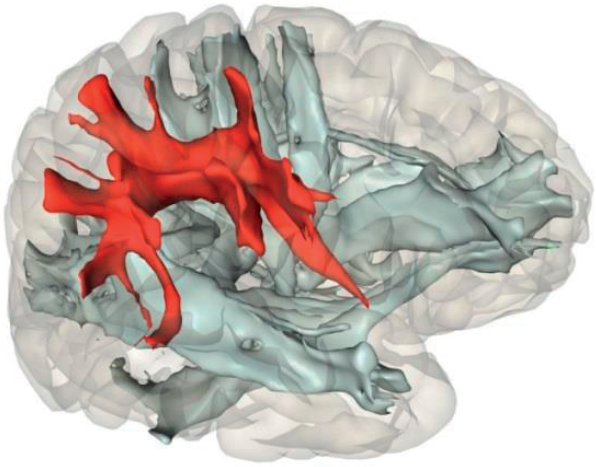

Figure 2. Tractographic reconstruction of the right superior longitudinal fasciculus, sagittal view.

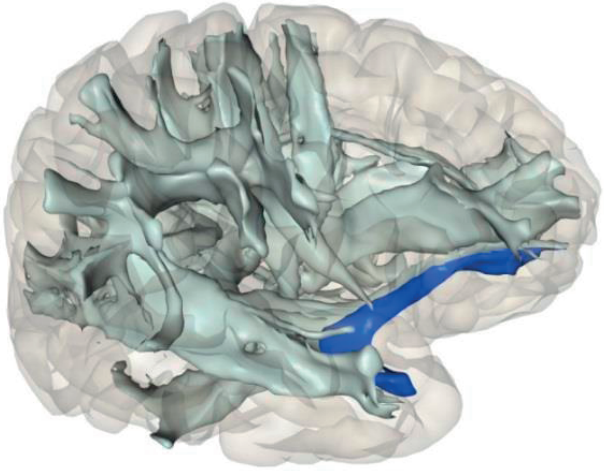

Figure 3. Tractographic reconstruction of the right uncinate fasciculus, sagittal view.

Finally, we performed VBA on the white matter tracts to examine whether specific tract-subregions showed primarily associations with worse hearing acuity. FA and MD in the voxel-based analysis were not associated with hearing acuity on both the pure-tone audiogram and the DIN-test.

DISCUSSION

Our objective was to investigate the association between brain white-matter micro-structure and hearing acuity in middle-aged and older adults in a large population-

based study. We found that poorer white-matter microstructure, in particular in association tracts, was significantly associated with worse hearing acuity. Altered white-matter microstructure in the right superior longitudinal fascisulus and the right uncinate fasciculus were associated with worse hearing acuity, when differentiating for the white-matter tracts in the left and right hemisphere. Progressive aging did not seem to be an effect modifier. In the VBA there were no single voxels in the white-matter tracts that were significantly associated with hearing acuity. Our results contribute to the discussion on how white-matter microstructure and hearing acuity are related. We found an association in specific auditory and language-related tracts. This could argue against the "common cause hypothesis". Otherwise, we would have expected more widespread changes throughout the brain. Moreover, we corrected our analyses for potential confounders and possible components of the "common cause hypothesis", such as age and hypertension. The fact that we still found significant associations between poorer white-matter microstructure and worse hearing acuity makes the "common cause hypothesis" as the main explanation less likely. We acknowledge that we might not have included several unknown confounders. Altered white-matter microstructure was both associated with worse hearing on the pure-tone audiogram as well as worse hearing on the DIN-test, which reflects central auditory processing and cognitive skills.[41] The brain alterations may thus have an effect on higher auditory and cognitive functions. This would plead for the "information-degradation hypothesis" over a mere loss of sensory deprivation with worse hearing. To further explore the stated hypotheses, a comparative neuroimaging study in hearing impaired participants with or without hearing aids may help narrow possible pathways. Different white-matter tracts have a variable susceptibility to age-related structural decline.[10] This could be caused by the location and function of the tracts. It also suggests that different tracts may play a different role in age-related diseases. We found that primarily association tracts, among these the superior longitudinal fasciculus and uncinate fasciculus, were related to hearing acuity. Association tracts connect the different cortical regions of the same hemisphere and are typically located in watershed areas, implying that their blood supply relies on small and deep lenticulostriate arteries. Association tracts may therefore be more vulnerable to insults and vascular damage.[42] The superior longitudinal fasciculus connects the frontal lobe with the temporal, parietal and occipital lobe. Multiple processes, such as language, emotion, and attention have been ascribed to the superior longitudinal fasciculus.[43] The uncinate fasciculus is an association tract that connects the limbic regions in the frontal lobe to the temporal lobe.[44] Its function is not exactly clear, however it seems to be involved in limbic tasks such as emotional processing and memory, including linguistic-related tasks such as naming people[45], semantic processing such as mnemonic associations[46] and better overall language development in children.[47] This is interesting, since we found an association with the

uncinate fasciculus and our speech-in-noise test. A lower FA in the right superior longitudinal fasciculus in hearing impaired participants was also found by Husain et al.[7] They also found associations with the inferior fronto-occipital tract, the corticospinal tract, and the anterior thalamic radiation. However, the authors only published p-values and no raw data, making direct comparison of effect sizes not possible. They did not find an association with the uncinate fasciculus. They did not perform a test on speech recognition in noise, such as the DIN-test, for which we primarily found an association with the uncinate fasciculus. This association could suggest that this tract is involved in higher order auditory function, including certain verbal memory functions needed to recall the digits in noise. Our second objective was to investigate the effect of aging on the association between white-matter microstructure and hearing acuity. We hypothesized a possible progression of white matter damage in worse hearing acuity with age. Besides correcting for age as a possible confounder in multivariable models 1 and 2, we also stratified our results between middle-aged and older participants to investigate if age is a possible effect modifier. We found no significant interaction, despite the fact that increased FA was significantly associated with a worse outcome on the DIN-test in the older group, whereas in the middle-aged group, this significant association was found in the pure-tone thresholds. Thus, progressive aging does not seem to act as an effect modifier. Profant et al. likewise noticed the differences in the relation between FA and hearing acuity among younger and older participants.[18] Although they compared their older group with a much younger group (mean age 67.9 vs. 24.3) than ours, they also did not find a significant effect. We suggest further research on this relation by performing longitudinal studies, since cross-sectional studies do not allow age changes within individuals to be studied. To our knowledge, we performed the largest study so far on tract-specific white-matter microstructure and hearing acuity. Furthermore, we tried to optimize the design. First, we investigated the whole brain instead of the central auditory system and thereby provided an overview of the brain. Second, we explored both peripheral and central hearing function. A pure-tone audiogram reflects more on the peripheral auditory function, whereas a speech-in-noise test informs on higher functions of the auditory system. Third, the tract-specific measurements were performed with fully automated and publicly available methods.[10] Finally, we corrected for cognition and cardiovascular risk factors.[19] Still, our study has several limitations. Within the tracts that we have studied, there was no specific auditory tract. This we tried to preempt by additionally performing an analysis on the voxel level using voxel-based morphometry. No significant voxels were found when we used 90% probability thresholds to define the tract templates (corresponding voxels had to belong to a tract in 90% of the participants). When lowering these thresholds to 10%, we found significant voxels in areas that belong to the right superior fasciculus and right inferior longitudinal fasciculus. However, this

means that in only 10% of the participants this was a predefined white-matter tract by the anatomical template. We made the choice for a 90% threshold so we were sure that we looked at white-matter tracts and not at voxels possibly belonging to other brain areas. An explanation for finding different results with the tract-specific and voxel-based analysis may be that due to multiple comparisons corrections, the threshold for the voxel-based analysis is too conservative. To detect significant voxels, a bigger sample size would be required. To decrease the number of tests, another method with low resolution can be used, such as for example tract profiles estimation[48] Third, our study was performed with 25 diffusion gradient directions, and this may have lowered the precision to detect crossing fiber populations. However, probabilistic tractography was performed with a good reproducibility of 0.89.[32] Therefore, we are confident that we could reconstruct the tracts of our interest accurately. Unfortunately, it was not possible to differentiate in our specific-tract data for subcomponents, for example, the 3 segments of the SLF that are presumed to have different functions.[49] Finally, the study design is cross-sectional, making it impossible to state a conclusion on the direction of the effect. Therefore, longitudinal research is required.

CONCLUSION

In 2562 participants of the Rotterdam Study, poorer white-matter microstructure was associated with worse hearing acuity, specifically in the right superior longitudinal fasciculus and uncinate fasciculus. Progressive aging was not found to be an effect modifier.

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SUPPLEMENTAL MATERIAL