Tinnitus and its central correlates: a neuro-imaging study in a large ageing population

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ABSTRACT

Objective

To elucidate the association between tinnitus and brain tissue volumes and white matter microstructural integrity.

Methods

2,616 participants (mean age 65.7 years [standard deviation: 7.5]; 53.9% female) of the population-based Rotterdam Study underwent tinnitus assessment (2011-2014) and magnetic resonance imaging (MRI) of the brain (2011-2014). Associations between tinnitus (present vs absent) and total, grey, and white matter volume and global white matter microstructure were assessed using multivariable linear regression models adjusting for demographic factors, cardiovascular risk factors, depressive symptoms, MMSE score and hearing loss. Finally, we assessed potential regional grey matter density and white matter microstructural differences on a voxel-based level again using multivariable linear regression.

Results

Participants with tinnitus (21.8%) had significantly larger brain tissue volumes (difference in standard deviation: 0.09 [95% CI: 0.06, 0.13]), driven by larger white matter volumes (difference: 0.12 [95% CI: 0.04, 0.21]) independent of hearing loss. There was no association between tinnitus and grey matter volumes nor with global white matter microstructure. On a lobar level, tinnitus was associated with larger white matter volumes in each lobe, not with grey matter volume. Voxel-based results did not show regional specificity.

Conclusion

We found that tinnitus in older adults is associated with larger brain tissue volumes, driven by larger white matter volumes, independent of age and hearing loss. Based on these results, it may be hypothesized that tinnitus has more of a neurodevelopmental origin potentially increasing the risk of developing future tinnitus in people with relatively larger brain tissue volumes from a young age onwards.

BACKGROUND

Tinnitus is a poorly understood and common disorder, often debilitating in the daily life of people with tinnitus.[2] The disorder can be characterized by the perception of a sound while there is no objective corresponding external sound source.[3, 4]
Hearing loss is suggested to be one of the most important risk factors for tinnitus: 90% of the people with chronic tinnitus have some form of hearing loss and the acoustic characteristics of the tinnitus sound correspond to the region of hearing loss.[2, 3, 5, 6] However, several observations indicate that tinnitus also has a central component to its pathogenesis, regardless of the peripheral damage that might trigger it.[7] Moreover, about 10% of individuals with tinnitus have normal hearing abilities.[2, 3] Recently, interest in the association between brain volume and brain function and tinnitus has increased. However, observed findings are often contradictory, some reporting regional cortical thickness reductions and functional alterations in individuals with tinnitus whereas other studies do not find significant associations.[4-13] These inconsistencies might be explained by high heterogeneity of individuals with tinnitus, differences in sample selection, imaging methodology and data analysis, and relatively small sample sizes. Moreover, previous studies mostly focused on auditory regions in the brain or the limbic system, disregarding potential whole brain associations.[3]

Therefore, the aim of this study was to assess the association between tinnitus and brain tissue volumes and white matter microstructure in a large population-based sample. Furthermore, we explored the association between tinnitus and the brain independent of hearing loss, to possibly disentangle peripheral versus central components contributing to prevalent tinnitus.

METHODS

Study setting and population

This cross-sectional study is embedded in the Rotterdam Study, a prospective, population-based study initiated in 1989 that investigates determinants and consequences of ageing.[14] The entire study population consists of 14,926 individuals aged ≥45 years from the Ommoord area, a suburb of Rotterdam, the Netherlands, who undergo extensive examinations at the research centre at study entry and subsequent visits every 3 to 4 years.

For this study, 4,773 participants who visited the study centre between 2011 and 2014 for initial or re-examinations underwent home interview on the presence or absence of tinnitus. Of the 4,151 participants with available tinnitus data, 2,661 participants also had MRI scanning of the brain (2011 – 2014). The median time interval between tinnitus

assessment and MRI scanning was 4.0 months (SD: 3.5). We excluded participants with cortical brain infarcts on MRI (N = 45), leaving a total of 2,616 participants for the current analysis.

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). All participants provided written informed consent to participate in the study.

Tinnitus assessment

Tinnitus was assessed during a home interview. Participants were asked if they experience or recently have experienced sounds in the head or in the ears, without an objective external sound source being present. Possible answers were: no, never; yes, less than once a week; yes, more than once a week but not daily; yes, daily.[14] For the current study, tinnitus was investigated as a binary variable; not present (no, never; yes, less than once a week) or present (yes, more than once a week but not daily; yes, daily). Because of the heterogeneity of the origin, and often temporary character of tinnitus present less than once a week, this was not recorded as prevalent tinnitus.

Magnetic resonance imaging

Brain MRI was performed on a 1.5-tesla MRI scanner with a dedicated 8-channel head coil (software version 11x; General Electric Healthcare, Milwaukee, WI).[15] The entire scan protocol and sequence details have been described elsewhere.[15]

Brain tissue volumes

For brain tissue volumes, T1-weighted, proton density-weighted, and the fluid-attenuated inversion recovery scans were used for automated segmentation of supratentorial grey matter, white matter, cerebrospinal fluid (CSF), and white matter hyperintensities.[16] Total brain tissue volume was the sum of grey matter, normal-appearing white matter, and white matter hyperintensity volume. Supratentorial intracranial volume was estimated by summing grey matter and white matter (normal-appearing white matter and white matter hyperintensity volume) and CSF volumes.[15] A multi-atlas approach was used to obtain lobar brain volumes (frontal, parietal, temporal, occipital) from all participants.[17]

White matter microstructural integrity

To obtain microstructural measures, diffusion tensor imaging (DTI) was used. A single shot, diffusion weighted spin echo echo-planar imaging sequence was performed with maximum *b* value of 1,000 s/mm^2 in 25 noncollinear directions; 3 b_0 volumes were acquired without diffusion weighting. Using a standardized processing pipeline, diffusion data were preprocessed.[18] From this (in combination with the tissue segmentation),

we derived global mean fractional anisotropy (FA) and mean diffusivity (MD) in the normal-appearing white matter. FA is the degree of anisotropy in the normal-appearing white matter and is given as a ratio ranging from 0 (isotropic or non-directional) to 1 (unidirectional). MD is expressed in square millimetres per second.

Voxel based morphometry of white matter tracts

We performed a voxel-based analysis of diffusion tensor MRI data using FSL software for preprocessing.[19] 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, a Rotterdam Study specific tract-atlas was created.[19] White matter tract segmentation masks of every participant were registered to Montreal Neurological Institute (MNI) template in the same way as FA and MD maps and then merged to one tract probability atlas image.[19] To map voxels from voxel-based analysis, a 10% probability cut-off was used to define tract boundaries microstructure.

Voxel based morphometry of grey matter density

Using an optimized protocol with FSL software, voxel-based analysis of the grey matter was performed.[19] Grey matter density maps derived from T1-weighted images were nonlinearly registered to the MNI template. A spatial modulation procedure was applied to preserver local grey matter volume, i.e. voxel densities were multiplied by the Jacobian determinants of transformation field. Subsequently, images were smoothed using an isotropic Gaussian kernel of 3 mm (full width half maximum 8 mm). The location of the voxels were defined based on Hammer atlas segmentation.[20]

Covariates

Educational level was categorized as lower, middle, or higher education. Height (meter) and weight (kilograms) were measured and body mass index (kg/m^2) was calculated. Systolic and diastolic blood pressure were measured twice using a random sphygmomanometer. Hypertension was defined as systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 90 mm Hg, and/or the use of blood pressure-lowering medication.[14] Using an automatic enzymatic procedure, serum total cholesterol and high-density lipoprotein cholesterol were measured from fasting blood samples. Hypercholesterolemia was defined as total cholesterol concentration ≥ 6.2 mmol/L and/or the use of lipid-lowering medication.[14] Self-reported smoking data were categorized into never, former, and current smoking. Alcohol consumption, in grams per day, was assessed through self-report by means of the Food-Frequency Questionnaire. The LASA Physical Activity Questionnaire was used to assess the amount of physical activity, recalculated into metabolic equivalent of task hours per week.[14] The MMSE was administered during home interview to assess global cognitive functioning.[14] To assess depressive symptoms,

the Center for Epidemiological Studies Depression scale was used. To determine hearing levels in decibel (dB), pure tone audiometry was used according to the ISO-standard 8253-1,[14] measured on different air conduction frequencies (0.25-8 kilohertz).

Statistical analysis

First, we investigated whether characteristics differed between participants with and without tinnitus, using T-tests, χ^2-tests and Mann-Whitney U-Tests when appropriate. Second, we explored the association of tinnitus with brain tissue volume (total, white matter, grey matter) and global white matter microstructural integrity (FA and MD) using multivariable linear regression models. In the first model we adjusted for age, sex, education, hearing loss, and intracranial volume (to adjust for intra-individual differences in head sizes). The second model was additionally adjusted for smoking, alcohol, physical activity, body mass index, hypertension, hypercholesterolemia, depressive symptoms and MMSE-score. Third, we performed a similar multivariable linear regression analysis investigating the association of tinnitus and lobar grey and white matter volume (frontal, temporal, parietal, occipital lobe) for the left and right hemisphere separately. Fourth, we performed the same multivariable linear models for the association between tinnitus and every voxel of the brain measures in the VBM analysis. It is important to note that, even though we expect that potential brain differences occur before tinnitus onset, we present our analyses and results with tinnitus as the determinant and brain measures as the outcome. Since the design of the current study is cross-sectional, results can be interpreted both ways, and we believe presenting results in the current order facilitates interpretation.

In sensitivity analyses, we explored whether results between tinnitus and brain volumes differed by degree of hearing loss (normal hearing: 0 – 20 dB; mild hearing loss: 20 – 40 dB; moderate/severe hearing loss: >40 dB). Next, to disentangle potential peripheral involvement, we used similar multivariable models in a sub-group of participants (N = 355) whom did not have a hearing threshold level above 20 dB on any of the measured hearing frequencies. Finally, we stratified by sex.

IBM SPSS statistics version 24.0 (IBM Corp, Armonk, NY, USA) was used for data handling and R statistical software version 3.5.1 was used for analyses. A p-value < 0.05 was considered statistically significant in the analyses between tinnitus, brain tissue volumes and white matter microstructure. For VBM, as the voxels throughout the brain are correlated, the actual number of independent tests was calculated using 10,000 permutations. The significant p-value threshold for $\alpha = 0.05$ was estimated separately for FA, MD and grey matter: 5.91×10^{-8} , 6.49×10^{-8} and 2.99×10^{-7} respectively.

RESULTS

Baseline characteristics are described in Table 1. Mean age was 65.7 years (standard deviation (SD): 7.5), 53.9% was female. Tinnitus was present in 21.8% of the study population (men: 51.8%; women: 48.2%, p-value: 0.002). Participants with tinnitus had a higher hearing threshold than those without tinnitus (28.8 dB (SD: 17.1); 22.5 dB (SD: 14.5) respectively, p-value: <0.001).

Table 1. Population characteristics

	Total sample (N = 2,616)	Participants with tinnitus (N = 570; 21.8%)	Participants without tinnitus (N = 2,046; 78.2%)	p-value
Age, years	65.7 (7.5)	65.7 (7.3)	65.8 (7.6)	0.789
Age, range	51.8-97.8	51.9-91.7	51.8-97.8	
Female, %	53.9	48.2	55.5	0.002
Hearing loss, dB	27.0 (15.3)	28.8	25.7	<0.001
Degree of hearing loss, %				<0.001
Normal: <20 dB	39.4	26.3	43.1	
Mild: 20-40 dB	46.3	51.1	45.0	
Moderate/severe: >40 dB	14.3	22.6	11.9	
Body mass index, kg/m^2	27.3 (4.0)	27.4 (4.0)	27.2 (4.0)	0.396
Education level, %				0.770
Primary	6.8	7.7	6.6	
Lower	35.4	35.6	35.6	
Middle	30.6	30.9	30.5	
Higher	26.5	26.5	26.5	
Smoking, %				0.003
Never	32.6	26.8	34.3	
Past	50.8	55.2	49.6	
Current	16.2	17.9	15.8	
Physical activity, MET[a]	46.5 (18.8, 85.3)	43.8 (18.9, 82.0)	46.9 (18.8, 85.8)	0.374
Alcohol, g/day[a]	8.0 (1.4, 19.0)	6.6 (1.1, 18.5)	8.3 (1.4, 19.1)	0.355
Hypertension, %	65.6	65.6	65.4	0.940
Hypercholesterolemia, %	51.9	54.4	51.3	0.127
MMSE <24, %	1.5	1.8	1.4	0.073
Depressive symptoms, %	8.6	10.5	8.1	0.487

Values are mean (standard deviation (SD)) for normally distributed continuous variables, median[a] (interquartile range) for non-normally distributed continuous variables. Values are percentages for dichotomous variables. dB: decibel. kg: kilogram. m: meter. MET: metabolic equivalent of task. g: gram. MMSE: Mini-Mental State Examination. Tinnitus was defined as a binary variable; either not present (no, never; yes, less than once a week) or present (yes, more than once a week but not daily; yes, daily). T-test were used for normally distributed variables, χ^2-test for dichotomous variables, and Mann-Whitney U-Test for non-normally distributed variables to see whether characteristics were significantly different ($p<0.05$) between participants with and without tinnitus.

Global brain tissue volumes and white matter microstructural integrity

We found that participants with tinnitus had statistically significantly larger brain tissue volumes (difference in SD brain tissue volume in participants with tinnitus as compared to participants without tinnitus: 0.07 [95% CI: 0.03, 0.10]) (model 1, Table 2), which was driven by larger white matter volume (difference: 0.12 [95% CI: 0.05, 0.19]) (model 1, Table 2). Additionally adjusting for other relevant confounders (model 2) did not change the effect estimates (difference total brain tissue volume: 0.09 [95% CI: 0.06, 0.13]; difference white matter volume: 0.12 [95% CI: 0.04, 0.21]) (Table 2). We did not find statistically significant associations between tinnitus and grey matter volume and white matter microstructural integrity (Table 2).

Table 2. The association between tinnitus and brain tissue volume and white matter microstructural integrity

		Total brain volume	Grey matter volume	White matter volume	Fractional anisotropy	Mean diffusivity
		Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)
Tinnitus; present versus absent	Model 1	**0.07 (0.03, 0.10)**	-0.02 (-0.08, 0.04)	**0.12 (0.05, 0.19)**	**0.00 (0.00, 0.00)**	0.00 (0.00, 0.00)
	Model 2	**0.09 (0.06, 0.13)**	0.02 (-0.05, 0.09)	**0.12 (0.04, 0.21)**	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)

Difference represents the difference in SD brain tissue volume (total, grey matter, white matter) or the difference in SD white matter microstructural integrity (fractional anisotropy, mean diffusivity) in participants with tinnitus as compared to participants without tinnitus. SD: standard deviation. CI: confidence interval. Model 1: adjusted for age, sex, education, hearing loss and intracranial volume. Model 2: additionally adjusted for smoking, alcohol intake, physical activity, body mass index, hypertension, hypercholesterolemia, depressive symptoms, and MMSE-score. Significant effect estimates ($p<0.05$) are indicated in **bold**.

Lobar brain tissue volumes

Associations for participants with tinnitus as compared to participants without tinnitus remained statistically significant on a lobar level (both left and right hemisphere) solely for larger white matter tissue volume across all the different lobes (frontal, temporal, parietal, and occipital) (Table 3; model 1 and 2). No statistically significant associations were found for grey matter volume on a lobar level (Table 3).

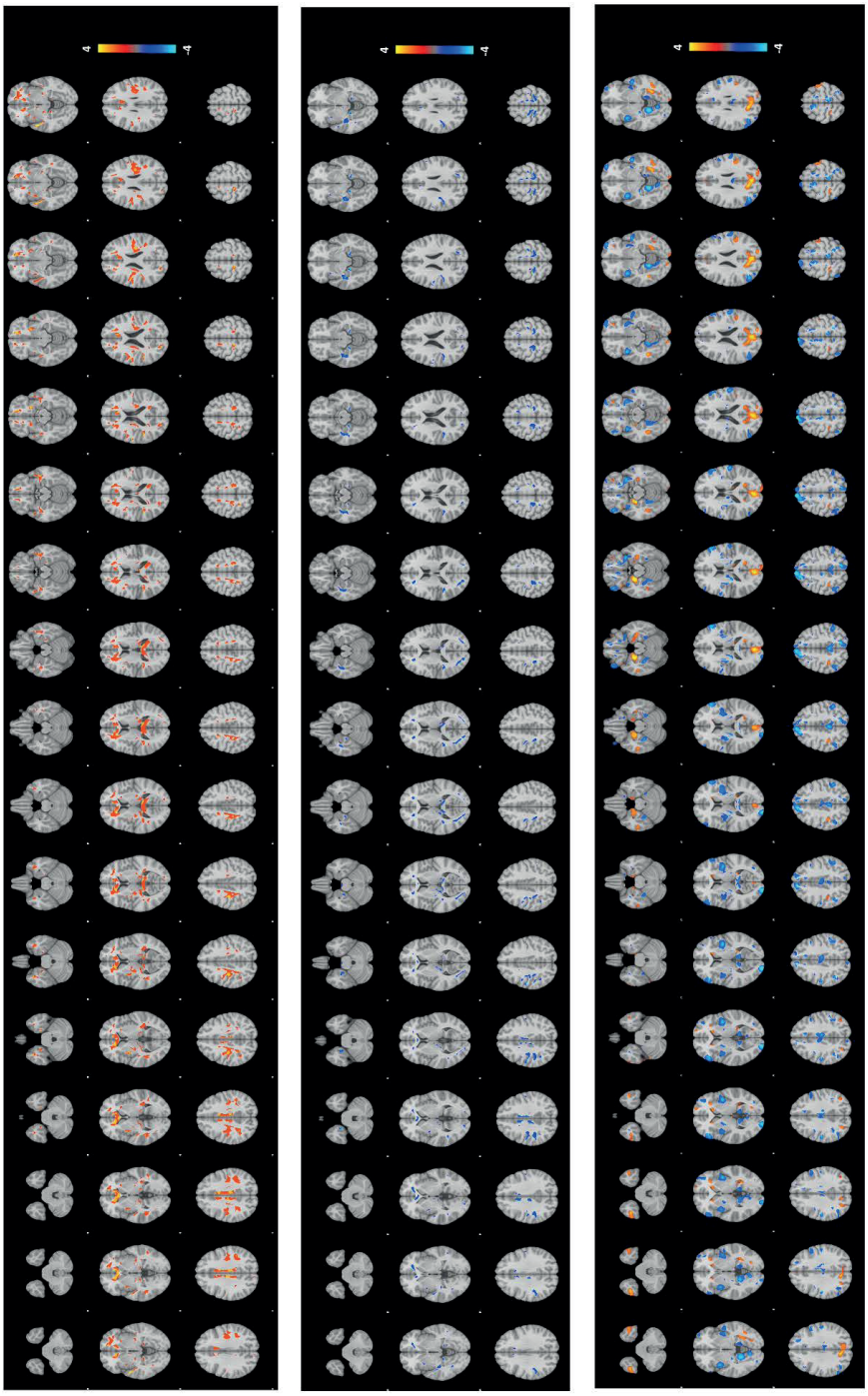
Voxel-based morphometry

We conducted exploratory voxel-based analysis to identify if tinnitus was associated with regional white matter integrity and grey matter density on a voxel level. The analyses showed that tinnitus was associated with higher FA as compared to participants without tinnitus in several white matter fibre bundles (Figure 1). However, these associations did not show regional specificity and were not statistically significant (Figure 1, Supplementary table 1). No statistically significant associations were found between tinnitus and voxel based white matter MD and grey matter density (Figure 1, Supplementary tables 2 and 3).

Table 3. The association between tinnitus and lobe specific tissue volumes

		Left frontal lobe	Right frontal lobe	Left temporal lobe	Right temporal lobe	Left parietal lobe	Right parietal lobe	Left occipital lobe	Right occipital lobe
		Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)
	Grey matter								
Tinnitus present versus absent	Model 1	-0.03 (-0.09, 0.04)	-0.03 (-0.10, 0.03)	0.01 (-0.04, 0.07)	0.01 (-0.05, 0.07)	-0.01 (-0.07, 0.06)	-0.02 (-0.08, 0.05)	0.01 (-0.06, 0.08)	-0.01 (-0.08, 0.05)
	Model 2	0.01 (-0.06, 0.08)	0.00 (-0.07, 0.07)	0.06 (-0.01, 0.13)	0.05 (-0.02, 0.12)	0.06 (-0.02, 0.14)	0.04 (-0.05, 0.12)	0.05 (-0.04, 0.13)	0.03 (-0.05, 0.11)
	White matter								
Tinnitus present versus absent	Model 1	**0.13 (0.06, 0.20)**	**0.13 (0.06, 0.20)**	**0.10 (0.03, 0.17)**	**0.12 (0.05, 0.19)**	**0.12 (0.04, 0.19)**	**0.13 (0.06, 0.20)**	**0.12 (0.04, 0.20)**	**0.11 (0.03, 0.19)**
	Model 2	**0.12 (0.03, 0.21)**	**0.13 (0.04, 0.21)**	**0.11 (0.02, 0.19)**	**0.13 (0.04, 0.22)**	**0.13 (0.04, 0.22)**	**0.14 (0.06, 0.23)**	**0.13 (0.03, 0.23)**	**0.12 (0.03, 0.22)**

Difference represents the difference in SD brain tissue volume in participants with tinnitus as compared to participants without tinnitus. SD: standard deviation. CI: confidence interval. Model 1: adjusted for age, sex, education, hearing loss and intracranial volume. Model 2: additionally adjusted for smoking, alcohol intake, physical activity, body mass index, hypertension, hypercholesterolemia, depressive symptoms, and MMSE-score. Significant effect estimates ($p<0.05$) are indicated in **bold**.



A B C

Figure 1.

Figure 1. A: Axial projection of white matter voxels: fractional anisotropy associated with tinnitus. Colours reflect the tendency of the association: blue for a negative direction (decrease of white matter fractional anisotropy in tinnitus), red for a positive direction (increase of white matter fractional anisotropy). **B:** Axial projection of white matter voxels: mean diffusivity associated with tinnitus. Colours reflect the tendency of the association: blue for a negative direction (decrease of white matter mean diffusivity), red for a positive direction (increase of white matter mean diffusivity). Higher white matter mean diffusivity indicates decreased white matter microstructural integrity. **C:** Axial projection of voxels: grey matter density associated with tinnitus. Colours reflect the tendency of the association: blue for a negative direction (decrease of grey matter), red for a positive direction (increase of grey matter). No statistically significant associations were found (see supplementary tables for exact outcomes per area).

Table 4. The association between tinnitus and brain tissue volume and white matter microstructural integrity – stratified by degree of hearing loss

		Total brain volume	Grey matter volume	White matter volume	Fractional anisotropy	Mean diffusivity
		Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)	Difference in SD (95% CI)
				Normal hearing (0 – 20 dB)		
Tinnitus present versus absent	Model 1	**0.07 (0.01, 0.12)**	-0.07 (-0.17, 0.02)	**0.17 (0.07, 0.28)**	0.00 (0.00, 0.00)	0.00 (-0.01, 0.00)
	Model 2	**0.10 (0.03, 0.17)**	-0.02 (-0.15, 0.11)	**0.18 (0.03, 0.32)**	0.00 (0.00, 0.00)	0.00 (-0.01, 0.00)
				Mild hearing loss (20 – 40 dB)		
Tinnitus present versus absent	Model 1	**0.08 (0.02, 0.14)**	-0.01 (-0.10, 0.08)	**0.14 (0.03, 0.25)**	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	Model 2	**0.10 (0.05, 0.16)**	0.02 (-0.08, 0.13)	**0.14 (0.00, 0.27)**	0.00 (0.00, 0.00)	0.00 (-0.01, 0.00)
				Moderate/severe hearing loss (> 40 dB)		
Tinnitus present versus absent	Model 1	0.04 (-0.04, 0.12)	0.04 (-0.09, 0.17)	0.02 (-0.13, 0.18)	0.00 (0.00, 0.01)	0.00 (-0.01, 0.01)
	Model 2	0.05 (-0.04, 0.14)	0.07 (-0.07, 0.22)	0.00 (-0.18, 0.18)	0.00 (0.00, 0.01)	0.00 (0.00, 0.01)

Difference represents the difference in SD brain tissue volume (total, grey matter, white matter) or the difference in SD for white matter microstructural integrity (fractional anisotropy, mean diffusivity) in participants with tinnitus as compared to participants without tinnitus. SD: standard deviation. CI: confidence interval. dB: decibel. Model 1: adjusted for age, sex, education, hearing loss and intracranial volume. Model 2: additionally adjusted for smoking, alcohol intake, physical activity, body mass index, hypertension, hypercholesterolemia, depressive symptoms, and MMSE-score. Significant effect estimates ($p<0.05$) are indicated in **bold**.

When stratifying by degree of hearing loss, similar associations between tinnitus and brain tissue volume were found (Table 4). In a subgroup of participants (N = 355; of whom 37 reported tinnitus) with no threshold above 20 dB on any of the measured frequencies, similar results were found as in the group with normal hearing; tinnitus was associated with larger brain tissue volumes, fully driven by larger white matter volumes (Supplementary table 4). Associations did not differ between males and females (Supplementary table 5).

DISCUSSION

In a large population-based sample of older adults we found that participants with tinnitus, independent of degree of hearing loss and age, had significantly larger brain tissue volumes as compared to participants without tinnitus. This association was entirely driven by larger white matter volumes. Tinnitus was not associated with grey matter volume or global white matter microstructural integrity. Regional analyses on a lobar or voxel-based level did not show regional specificity for these findings.

There is a known strong relation between hearing loss and tinnitus.[1] As hearing loss has previously been associated with smaller brain tissue volumes and decreased white matter microstructure,[2, 3] we had expected similar results: an association between tinnitus and smaller brain volumes and compromised white matter microstructure. Conversely, we found that individuals with tinnitus had larger white matter volumes, which was also independent of hearing loss. These results suggest that tinnitus is not related with ageing processes such as neurodegeneration. Indeed, another study reported no associations between tinnitus and white matter volume changes. They suggested that decreased white matter volume may be explained by comorbid hearing loss, which is again largely determined by age.[4] In line with this, several other studies proposed that grey matter changes, which is also known to decrease with age,[5] are attributable to the age-related hearing loss rather than the tinnitus per se.[4, 6] In light of our results, it may be hypothesized that tinnitus is associated with neurodevelopmental aspects in earlier life. To put it differently, people with larger brain tissue volume from an early age onwards may be more at risk for tinnitus at later ages then people with smaller brain tissue volumes. To truly state whether tinnitus indeed has a neurodevelopmental origin, longitudinal research in children, adolescents and young adults with and without tinnitus is needed. One study in a middle-aged population with tinnitus (mean age: 59 years [SD: 8.3]) reported larger grey matter volumes of the left auditory cortex, thus indicating that larger brain volumes in individuals with tinnitus may already be present in middle-aged adulthood.[7] However, to our knowledge, no study has explored these associations in a younger population yet.

A meta-analysis on tinnitus and functional-MRI detected regions of aberrant neural activity mainly in the non-auditory brain regions, including the parahippocampus, insula, cerebellum, cuneus, and thalamus.[8] Interestingly, we found that tinnitus was associated with larger white matter volumes in every lobe, whereas it could be expected that especially the temporal lobe would have been associated with tinnitus as it encompasses the auditory cortex. Thus, our results, in accordance with above mentioned meta-analysis, might point towards a more generalized effect of tinnitus on the brain, or vice versa. Longitudinal data is needed on both brain measurements and tinnitus, including data on tinnitus duration and onset, to truly determine whether people with larger white matter volumes are more sensitive for tinnitus, or the other way around, that tinnitus leads to cortical reorganization and aberrant neural activity.

Moreover, though not statistically significant, we found that tinnitus tended to relate to increased white matter microstructure of the white matter tracts based on a VBM analysis. Previous VBM studies mostly found associations between the prevalence of tinnitus and reduced cortical thickness in the bilateral temporal and frontal lobes,[9] reduced white matter volumes[10] and decreased white matter integrity.[9] Yet, we could not replicate these findings. Results between studies remain conflicting, probably due to methodological differences such as participant selection (clinical populations versus the general population), small sample sizes and focusing on specific regions of interest of the brain instead of whole brain analyses. Furthermore, most previous studies failed to appropriately adjust for effects of ageing, which may have led to residual confounding by age and its associated neurodegeneration.[5]

Another key feature of our analysis is that we explored associations between tinnitus and the brain taking into account the amount of hearing loss to disentangle possible central versus peripheral components contributing to tinnitus. Our results indicated that the association between tinnitus and brain tissue volumes is independent of hearing loss. This association attenuated in a sub-sample of participants with no hearing threshold above 20 dB on any of the measured hearing frequencies, again supporting a strong central component of tinnitus. It has been hypothesized that a peripheral trigger is associated with the onset of tinnitus.[11] However, based on our results it may be argued that central processes play a large role in maintaining tinnitus or being at risk for developing tinnitus. Still, we cannot infer on what causes tinnitus; whether there is one sole pathophysiological mechanism or multiple. Longitudinal studies are needed to unravel whether the incidence of tinnitus is associated with either peripheral or central processes or with both.

Strengths of our study included the large population-based sample, the (quantitative) assessment of brain structure and microstructure using imaging and the availability of extensive information on potential confounding factors. A limitation of the current study is its cross-sectional nature, hampering the possibility to infer causality between

determinant and outcome. Moreover, due to incomplete data we could not investigate the severity of the tinnitus complaints. Nor did we have information on the time since tinnitus onset and which ear was affected. On top of this, even though we extensively adjusted for potential confounders, residual confounding may still be present. Moreover, even though a 1.5 tesla MRI scanner is widely used, both in research and in clinical settings, a higher field strength would have the advantage to more sensitively image relatively small structures.

To conclude, we found that tinnitus is associated with larger brain tissue volumes, driven by larger white matter volumes, independent of hearing loss and age. Thus, it may be hypothesized that tinnitus has more of a neurodevelopmental origin potentially increasing the risk of developing future tinnitus in people with larger brain tissue volumes from a young age onwards. Future (longitudinal) population-based studies are warranted to elucidate the role of peripheral damage and central processes in the pathophysiology of tinnitus.

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