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Elevated Pure Tone Thresholds Predict Altered Microstructure in Cortical Areas Related to Auditory Processing and Attentional Allocation

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Abstract

Background: Hearing loss is associated with cognitive decline and increased risk for Alzheimer's disease, but the basis of this association is not understood.

Objective.—To determine whether hearing impairment is associated with advanced brain aging or altered microstructure in areas involved with auditory and cognitive processing.

Methods: 130 participants, (mean 76.4±7.3 years; 65% women) of the Rancho Bernardo Study of Healthy Aging had a screening audiogram in 2003-2005 and brain magnetic resonance imaging in 2014-2016. Hearing ability was defined as the average pure tone threshold (PTA) at 500, 1000, 2000 and 4000 Hz in the better-hearing ear. Brain-predicted age difference (brain-PAD) was calculated as the difference between predicted age based on a validated structural imaging biomarker of brain age, and chronological age. Regional diffusion metrics in temporal and frontal cortex regions were obtained from diffusion-weighted MRIs. Linear regression analyses adjusted for age, gender, education, and health-related measures.

Results: PTAs were not associated with brain-PAD (β= 0.09; 95% CI: −0.084 to 0.243; p=0.34). PTAs were associated with reduced restricted diffusion and increased free water diffusion primarily in right hemisphere temporal and frontal areas (restricted diffusion: β's= −0.21 to −0.30; 95% CIs from −0.48 to −0.02; p's< 0.03; free water: β's= 0.18 to 0.26; 95% CIs 0.01 to 0.438; p's< 0.04).

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CONFLICTS OF INTEREST

Donald J Hagler Jr is listed as an inventor on US Patent 9,568,580, 2017, "Identifying white matter fiber tracts using magnetic resonance imaging (MRI)." Other authors report no conflicts of interest.

Conclusions: Hearing impairment is not associated with advanced brain aging but is associated with differences in brain regions involved with auditory processing and attentional control. It is thus possible that increased dementia risk associated with hearing impairment arises, in part, from compensatory brain changes that may decrease resilience.

Keywords

Alzheimer's disease; dementia; hearing impairment; MRI; neuroimaging

INTRODUCTION

Hearing loss is prevalent among older adults, affecting more than 60% of US adults over the age of 70 years [1]. In addition to detrimental effects on quality of life [2], hearing loss is associated with steeper cognitive decline with age and increased risk of Alzheimer's disease and related dementias [3-11]. Due to its high prevalence, hearing impairment has been reported to have the largest population-attributable risk for dementia of potentially modifiable risk factors, accounting for 8% of dementia cases [12, 13]. Whether hearing impairment is a modifiable risk factor for dementia depends on the nature of the underlying association, which has not yet been established [14]. Multiple hypotheses have been proposed [15]. According to the common-cause hypothesis, sensory and cognitive impairment both arise from general age-related physiological changes independently of each other [16, 17]. If true, intervening on hearing would not affect risk to cognitive health. Two other hypotheses, which are not mutually exclusive, postulate a causal role of hearing impairment in cognitive decline [14, 18-20]. In the sensory deprivation hypothesis, loss of afferent input from the cochlea leads to reductions in synaptic density and axonal loss in primary auditory cortical areas in the temporal lobe, as well as in cortical areas that receive projections from primary auditory cortex. According to the cognitive load hypothesis, the increased effort required to decipher degraded auditory stimuli leads to altered activity and cortical reorganization in brain areas beyond those involved in auditory processing, as effort is shifted towards processing auditory information [20, 21]. Brain changes arising from sensory deprivation or reallocation of resources may impair cognitive function and decrease resilience to other pathologies that accumulate with age, which may be prevented or mitigated by intervening on hearing ability.

Structural imaging studies have shown that hearing impairment is associated with global and regional brain differences [15], including reduced volume in primary auditory cortex [22, 23], and increased rate of whole brain and regional temporal lobe volume loss [24, 25]. Hearing impairment has also been associated with thinner anterior cingulate cortex and middle frontal gyrus in some studies [26, 27], as well as with smaller whole brain volumes [28]. To obtain further insight into brain differences associated with hearing impairment among older adults, we investigated whether elevated pure tone hearing thresholds were associated with a structural imaging biomarker of brain aging. Studies examining structural imaging biomarkers of brain age have reported that older brain-predicted age than chronological age (brain-predicted age difference or brain-PAD) is associated with earlier mortality, higher chronic disease burden, and lower scores on cognitive and physical

function tests [29, 30]. If hearing impairment reflects advanced brain aging, we would expect higher auditory thresholds to be associated with older brain-PAD.

We also examined whether hearing impairment may be associated with microstructural changes in brain regions related to auditory processing and effortful control of attention. Most prior studies on the association of hearing with brain measures have used morphometric measures to assess changes in morphology, but neural reorganization in response to sensory deprivation or enhanced processing demands may result in more subtle changes. We used a sensitive neuroimaging measure of brain cytoarchitecture, the multi-compartment diffusion MRI model restriction spectrum imaging (RSI) [31]. RSI measures the magnitude and orientation of water diffusion in the brain along a spectrum of length scales from restricted, to hindered, to free water diffusion. The scale of restricted diffusion is consistent with constrained diffusion within intracellular spaces including neurites and cell bodies, and thus may be sensitive to changes in neural processing related to deprivation of input or to increased processing demands. We hypothesized that elevated auditory thresholds would be associated with differences in restricted diffusion in primary auditory cortex (transverse temporal gyrus), auditory association cortex including Wernicke's areas (superior temporal gyrus) and downstream association areas where auditory information is integrated with other information for speech and language processing (pars triangularis and pars opercularis in the inferior frontal gyrus) and for memory (hippocampus), as would be predicted by either the sensory deprivation or cognitive load hypotheses. To further evaluate the cognitive load hypothesis, we examined hearing-related differences in restricted diffusion in brain areas involved with the effortful allocation of attention (rostral anterior cingulate and middle frontal cortex). As a control, we investigated associations in a brain area not expected to differ by hearing thresholds, primary visual area in the pericalcarine cortex. Our primary analyses focused on restricted diffusion because we hypothesized that this measure may provide more sensitive detection of neuronal reorganization that may not manifest as gross differences in brain morphology or tissue volume loss. In secondary analyses we examined hearing-related differences in free-water isotropic diffusion, which characterizes cerebrospinal fluid and thus may be sensitive to tissue loss [31]. We also evaluated macroscopic differences in cortical thickness (or volume for the hippocampus) to determine whether hearing impairment is associated with evidence of gross atrophy in these regions.

MATERIALS AND METHODS

Participants

Participants included community-dwelling residents enrolled in the longitudinal Rancho Bernardo Study (RBS) of Healthy Aging who had hearing thresholds measured in a research clinic visit in 2003-2005 and underwent brain magnetic resonance imaging (MRI) during a research clinic visit in 2014-2016 (n=142). Complete imaging data (structural and diffusion-weighted) that passed quality assurance inspection were available for 131 adults. One participant lacked information on covariates, resulting in an analytic sample of 130 (age range 58 to 92 years, mean age 76.4 ±7.3; 65.4% women).

Study procedures were approved by the University of California, San Diego Human Research Protections Program Board and participants provided informed written consent prior to participation at each research visit (protocol number 130757).

Hearing Assessment

Hearing measurements were performed with a Welch-Allen portable audiometer without use of hearing aids (only 2 participants reported hearing aid usage). Ability to detect tones at frequencies of 500, 1000, 2000, and 4000 Hz, at thresholds of 40, 25, and 20 dB was determined for each ear. The quietest sound the participant could detect was assigned as the hearing level for that ear. If a participant was unable to hear the tone at 40 dB, measurement was stopped at that frequency and a value of 50 dB was assigned. The pure-tone average (PTA) threshold was calculated as the average threshold across the four frequencies for each ear. For sample description only, participants were categorized into those with normal (PTA ≤25 dB) or impaired (PTA >25) hearing (analyses of association of PTA with imaging outcomes treated PTA as a continuous variable). Subjective hearing was assessed with a brief questionnaire asking whether participants experienced difficulty hearing normal conversations.

Covariate Assessment

A standardized questionnaire was used to assess health status and behaviors including smoking (never/ever), alcohol intake (number of drinks per day), and physical activity (≥3 times/week, yes/no). Diabetes was ascertained based on self-report of a physician diagnosis, or use of diabetes medications. Prevalent cardiovascular disease was defined as self-report of physician-diagnosis of myocardial infarction, congestive heart failure, or transient ischemic attack. Blood pressure was measured twice in rested, seated participants; the mean of the two readings was used for analysis. Participants were considered hypertensive if they had an average systolic blood pressure ≥140, diastolic blood pressure ≥ 90 or were taking antihypertensive medication and reported a physician diagnosis of hypertension.

Imaging data acquisition

Imaging data were acquired on a 3.0 Tesla Discovery 750 scanner (GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased array head coil. The MRI sequence included a three-plane localizer; a sagittal 3D fast spoiled gradient echo T_1-weighted volume optimized for maximum gray/white matter contrast (TE=3.2 ms, TR=8.1 ms, inversion time=600 ms, flip angle=8°, FOV=24 cm, frequency=256, phase=192, voxel size=1×1×1.2 mm, scan time 8:27); and an axial 2D single-shot pulsed-field gradient spin-echo echo-planar imaging sequence (one b=0 volume plus b=500, 1500, 4000 s/mm^2 with 15 gradient directions for each non-zero b-value; TE=80.6 ms, TR=7 s, frequency=96, phase=96, FOV=24 cm, slice thickness=2.5 mm, scan time 6:34). An additional b=0 volume was collected prior to the diffusion sequence with reverse phase-encode polarity for B_0 distortion correction.

Brain-Predicted Age

Predicted age was calculated from T1-weighted MRI data using Cole's predicted brain age model [30, 32, 33] as we have previously described for this cohort [34]. Briefly, Cole's model applies an algorithm developed using Gaussian Processes Regression, implemented using the kernlab package in R, to relate MRI features to chronological age [32]. The model was trained on a sample of 3377 healthy adults aged 18-92 from seven large, publicly available datasets, and tested on a separate sample of 857 healthy adults, aged 18-90 years from those same datasets [32].

As we previously described [35], we used SPM12 to segment and normalize the T1-weighted MRI scans prior to using the Rnifti package in R to create vectors with mutually exclusive grey matter, white matter and cerebrospinal fluid tissue compartments. We then used the R kernlab package to quantify the 435 variables found by Cole to best predict chronological age and calculated the predicted age score for each participant. Visual quality control was conducted using FSL [36]. We subtracted chronological age from the brain-predicted age to obtain the brain-predicted age difference score (brain-PAD). Positive scores reflect older predicted than chronological age.

Regional Thickness and Diffusion Measures

MRI data were processed using an automated system combining tools developed in-house with FreeSurfer (http://surfer.nmr.mgh.harvard.edu), as previously described [37]. Briefly, imaging data were corrected for gradient nonlinearity distortions, dMRI data were also corrected for eddy current distortion, head motion, and B0-susceptibility distortion. Images were visually inspected for artifacts, and those containing uncorrectable artifacts were excluded. Gray matter, white matter, and CSF boundaries were identified on T_1-weighted images using FreeSurfer's automated cortical reconstruction. Regional cortical thickness was computed as the distance between the white matter and pial surfaces, with regions labeled according to the Desikan-Kiliany atlas. Hippocampal volume and estimated total intracranial volume were computed using FreeSurfer's volumetric segmentation.

Derivation of RSI metrics from dMRI data have been previously described for this cohort [38]. Briefly, after coarse pre-alignment to atlas images, the T_2-weighted b=0 volume from the dMRI scan was registered to T_1-weighted images using mutual information. Data were resampled to the original dMRI acquisition resolution using cubic interpolation, and a registration matrix was created to specify the rigid-body transformation between dMRI and T_1-weighted images. To minimize partial volume effects, cortical grey matter RSI metrics were sampled 0.8-2.0 mm from the gray/white matter boundary normal to the cortical surface, excluding or down-weighting voxels outside the cortical ribbon [39]. Our primary outcome measure was total diffusion in the restricted compartment [31], which combines restricted isotropic diffusion (0^{th} spherical harmonic), consistent with small cell bodies, with anisotropic restricted diffusion while accounting for crossing fibers (2^{nd} and 4^{th} spherical harmonics), consistent with axons and dendrites. Thus, total restricted diffusion estimates the aggregate fraction of presumed intracellular diffusion. We also examined isotropic free water diffusion as a sensitive measure of regional atrophy. These RSI measures were computed in eight bilateral cortical regions: transverse temporal cortex, superior temporal

cortex, pars triangularis, pars opercularis, hippocampus, rostral anterior cingulate, rostral middle frontal, and pericalcarine cortex.

Statistical analysis

Participant demographics were compared between individuals with normal or impaired (PTA >25 dB) hearing acuity using analyses of variance for continuous measures or chi-squared tests for categorical variables. Linear regression analyses were used to assess the effect of age and gender on the neuroimaging outcomes.

To examine whether hearing acuity predicted brain measures assessed approximately 10 years later, linear regression analyses were performed using average PTA threshold in the better-hearing ear (continuous) as the predictor with separate models for each outcome. Models adjusted for gender, education, age at time of MRI, smoking, physical activity, alcohol use, hypertension, diabetes, and prevalent CVD.

Participant characteristics were compared using IBM SPSS Statistics version 28.01.1. Regression analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC). Associations were interpreted based on uncertainty estimates (95% confidence intervals) for hypothesis testing [40].

RESULTS

Participant demographics as a function of hearing acuity are shown in Table 1. Half the sample (49%) had hearing impairment at the baseline visit. Participants with hearing impairment were older; more likely to be men, and to have hypertension. Although left and right ear PTA were correlated ($r=0.73$; $p < .001$); left ear thresholds were higher than right ear thresholds, (31.2 vs 29.0 dB; $t(13) = -2.22$; $p<.001$), and the better-hearing ear was more often the right (56.5%) than the left ear (21.4%; the remaining 22% had no difference in thresholds between the two ears). Differences in thresholds between the two ears were generally small (mean difference of 4.3 ±5.6 dB); only five participants met American Academy of Otolaryngology–Head and Neck Surgery definition for asymmetric hearing, with a 15 dB or higher threshold difference between the two ears. The better-hearing ear was the right ear for 4 of these 5 participants.

Brain PAD

MRIs were obtained an average of 10.2 years (±0.91; range 8.2-12.5 years) after hearing assessment. As previously reported for RBS participants [34], brain-predicted age correlated well with chronological age, $r = 0.73$ ($p<.001$) suggesting good model fit. Brain-PAD was not correlated with age ($r = -0.007$; $p = 0.94$), suggesting no age-related bias in the model. Brain-PAD did not differ by PTA ($\beta= 0.091$; 95% CI: −0.084 to 0.243; $p = 0.34$; see Figure 1).

Regional Microstructure

Table 2 shows the results for restricted and free water diffusion in the 8 bilateral brain regions. Scatter plots of the association of PTA thresholds with the diffusion measures are

shown in Supplement Figures S1 and S2. Restricted diffusion decreased with age in all regions except the anterior cingulate (Supplemental Table 1). There were no differences in restricted diffusion between men and women. In analyses adjusting for age, gender, and health-related covariates, restricted diffusion was lower with increasing hearing thresholds in all regions, but uncertainty intervals included the null for all regions except right hemisphere primary auditory cortex (transverse temporal), right inferior frontal areas (pars triangularis and pars opercularis), and bilateral rostral middle frontal gyrus. For both left and right hemisphere middle frontal cortex, each standard deviation (SD) increase in PTA threshold (i.e. each 8 dB increase in threshold) was associated with a 0.23 SD decrease in restricted diffusion (Table 2). PTA thresholds were not related to restricted diffusion in left or right pericalcarine cortex. Exclusion of the five participants with asymmetric hearing thresholds did not materially change the results.

Free water diffusion increased with age in all regions and was higher among men than women in several regions (Supplemental Table 1). In analyses adjusting for age, gender, and health-related covariates, elevated PTA thresholds were associated with increased free water diffusion in right hemisphere pars triangularis and pars opercularis, hippocampus, and rostral anterior cingulate (Table 2). Associations in corresponding left hemisphere regions were smaller, with confidence intervals including the null. PTA thresholds were not related to free water diffusion in pericalcarine cortex. Exclusion of the 5 individuals with asymmetrical hearing thresholds did not materially affect the results.

Cortical thickness decreased with age bilaterally in the superior temporal cortex and in left hemisphere transverse temporal, pars triangularis and middle frontal cortex; hippocampal volume decreased with age bilaterally (see Supplemental Table 1). Men showed thinner right hemisphere anterior cingulate cortex than women. Only the right hemisphere pars triangularis showed decreased thickness with increasing hearing thresholds ($\beta = -0.257$; 95% C.I. −0.462 to −0.086; p = .011); this association remained significant after excluding the 5 individuals with asymmetric hearing. There was suggestive evidence of bilateral hippocampal volume decreases with increased hearing thresholds (left: $\beta = -0.162$; 95% C.I. −0.327 to 0.003; p = .055; right: $\beta = -0.168$; 95% C.I. −0.337 to 0.000]; p = .050); with stronger associations after excluding the 5 participants with asymmetrical hearing thresholds (left: $\beta = -0.183$; p = .042; right: $\beta = -0.201$; p = .028)

DISCUSSION

In this sample of community-dwelling older adults, elevated hearing thresholds were not associated with an imaging biomarker of advanced brain age but were associated with microstructural differences in primary auditory cortex in the temporal lobe and language-related areas in the inferior frontal lobe. They were also associated with microstructural differences in areas of frontal cortex associated with effortful attentional control but were not associated with microstructure differences in primary visual cortex.

Our finding that a validated biomarker of brain aging was not associated with hearing impairment is consistent with a recent prior study by Rosemann et al. [27] that examined Cole’s brain age biomarker among a younger sample of adults (mean age 64.7) with

primarily mild high frequency hearing impairment [27]. Here we extend this finding to an older sample of adults including those with more severe hearing impairment, and with impairment in lower frequency ranges. Rosemann et al. [27] postulated that the brain age biomarker may only be sensitive to brain changes among diseases like schizophrenia and dementia that profoundly affect brain structure, not to the more subtle differences that could be related to hearing impairment. However, we, and others, have found significant associations of structural MRI-based brain age biomarkers with several factors that have more subtle associations with brain structure. For example, chronic disease burden, cigarette smoking, heavier alcohol consumption, decreased physical function and adverse events earlier in life have all been associated with older brain-predicted age diff, whereas greater physical activity and higher levels of education have been associated with younger brain-predicted age [30, 34, 35, 41-45]. Thus it is unlikely that the lack of association with hearing impairment reflects insensitivity of the biomarker; rather, it suggests that brain differences related to hearing impairment may be more regionally-specific, or may not be associated with macrostructural changes in areas most sensitive to changes with age.

We observed regionally-specific associations of microstructural measures with elevated auditory thresholds in the absence of macroscopic differences in cortical thickness. We found decreased restricted diffusion with increasing PTA thresholds in right hemisphere primary auditory cortex (transverse temporal gyrus), in areas of inferior frontal lobe involved with speech and language processing that receive primary and secondary projections from auditory cortex (pars triangularis and pars opercularis), and bilaterally in frontal lobe areas involved with effortful allocation of attention (rostral middle frontal gyrus), but not in anterior cingulate. These differences were significant after adjustment for age – which was associated with decreased restricted diffusion in all regions except the anterior cingulate; and for other demographic and health related covariates.

Increased free water diffusion, a measure sensitive to atrophy, increased with age in all regions, consistent with our prior report [46]. It also increased with increased PTA thresholds, independent of age and other covariates, in right hemisphere pars triangularis, anterior cingulate, and hippocampus. The right hemisphere pars triangularis was the only region to show macroscopic difference in cortical thickness with elevated hearing thresholds. There was also suggestive evidence of hippocampal volume decrease with increased hearing thresholds.

Our findings are broadly consistent with prior studies that have reported reductions in auditory cortex and temporal lobe volumes with hearing impairment [22-25]. Stronger associations in right hemisphere than in the left hemisphere has also been previously reported [22, 24]. The reason for this asymmetry is not understood. It may be related to the finding that the better-hearing ear was more often the right ear in our sample. With contralateral dominance of sensory processing, input to the left hemisphere may have been less degraded than input to the right hemisphere. However, between-ear differences in thresholds were small, and few participants met clinical criteria for hearing asymmetry. Differences in PTA thresholds between ears were not investigated by Lin et al. [24], whereas Armstrong et al. [11] found that, among middle-aged adults, right ear hearing loss was associated with volume loss in both right and left temporal regions; left ear

thresholds showed fewer significant associations. These studies speculated that rather than reflecting between-ear differences in thresholds, the left-hemisphere's role in speech and language may confer resilience to detrimental effects of hearing impairments [22, 24]. Of note, associations of restricted diffusion with hearing thresholds were of similar magnitude between left and right rostral middle frontal areas in our study. Middle frontal cortex plays an important role in executive function and effortful allocation of attention and these processes are less lateralized than speech and language processing.

In studies of UK Biobank participants, impaired hearing, as assessed with a speech in-noise test, was associated with reduced volumes in several brain areas, including temporal cortex, middle frontal cortex, and anterior cingulate area, as well as other brain regions related to cognitive processing [47, 48]. Performance on speech-in-noise tests can differ by cognitive ability as well as by elevated auditory thresholds [49], thus it is difficult to tease apart contributions from peripheral hearing loss to brain differences from contributions of cognitive or central auditory processing deficits. A smaller study of 71 adults, mean age 64 years, showed that high frequency hearing loss (in the 2 – 8 kHz frequency range) was associated with reduced volume of middle frontal cortex suggesting that peripheral hearing impairment may contribute to changes in brain areas related to effortful attention and executive function [27]. Although we did not find differences in cortical thickness in this region, we did observe decreases in restricted diffusion.

Fewer studies have reported associations of hippocampal measures with hearing thresholds. One large study of older adults aged 40-79, with equal representation across decades, reported reduced hippocampal volume with elevated pure tone thresholds [50]. However, age-related differences in hippocampal volumes may have contributed to these associations, given the large age difference, (about 12 years) between impaired and non-hearing impaired participants, which may not be fully controlled by covariate adjustment. In our sample of older adults, we observed suggestive evidence of hearing-related differences in hippocampus, limited to a small increase in free water diffusion, and no difference in restricted diffusion. In contrast, there were robust age-related differences in restricted and free water diffusion in the hippocampus, as well as reductions in hippocampal volume. Limitations of our study include the primarily White and middle to upper-middle class sample, thus results may not generalize to more diverse samples. MRI data were only available from a research visit 10 years after hearing was assessed, thus our study cannot address temporality of brain differences relative to onset of hearing impairment. As is common in epidemiological studies, hearing earing was measured with a screening audiogram, limited to four frequencies spanning the range of 0.5 – 4 KHz, a range critical for speech perception, with thresholds assessed only to a level of 40 dB. Thus, we do not have precise measures of pure tone thresholds to characterize the severity of hearing impairment and we lack information on high frequency hearing loss. We do not have sufficient power to determine whether associations differed according to whether left or right ear showed elevated thresholds. Finally, the physiological mechanisms underlying the hearing-related differences in restricted diffusion are unknown.

In summary, elevated pure tone thresholds among older adults were associated with microstructural differences in regions of temporal and frontal cortex associated with auditory

and speech processing, and in frontal lobe areas related to attentional control. Hearing impairment was not associated with a structural imaging biomarker of general aging. These findings contribute to the growing literature suggesting that hearing impairment is associated with regionally-specific changes in the brain that may occur due to sensory deprivation and the increase in effortful attention needed to process degraded auditory input. These changes may decrease resilience to pathologies that accumulate with age, impacting cognitive function and increasing dementia risk. This implies that interventions that can alleviate the increased cognitive load associated with hearing impairment may help reduce risk of cognitive decline and dementia associated with hearing loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

Sensory data, demographics, and covariates from the Rancho Bernardo Study of Healthy Aging are available through the study website: https://knit.ucsd.edu/ranchobernardostudy/. Derived neuroimaging metrics are available from the corresponding author.

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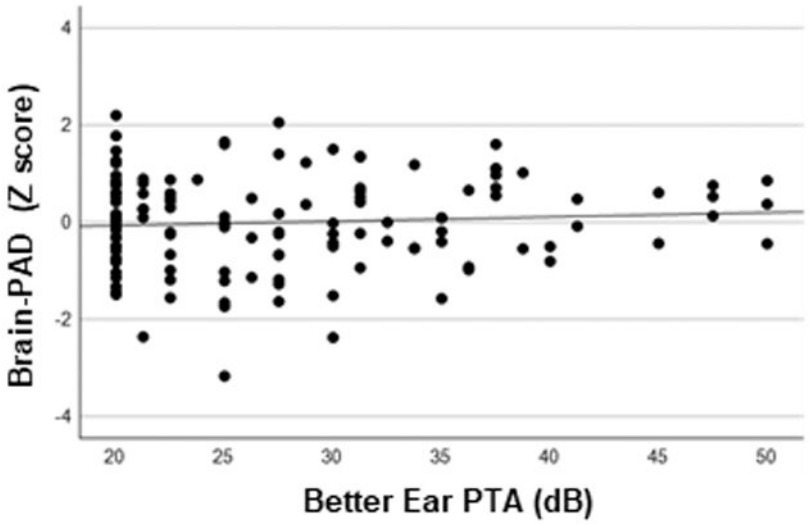

Figure 1.

Association of average pure tone thresholds (PTA) in the better hearing ear with brain predicted age difference (brain-PAD). Values are standardized residuals regressing on age, gender, years of education. smoking status, physical activity, alcohol use, hypertension, diabetes, and prevalent CVD.

Table 1.

Participant characteristics at time of MRI acquisition as a function of hearing status measured 10 years previously. The Rancho Bernardo Study of Healthy Aging. Values shown are number (percentage) unless otherwise indicated.

	PTA ≤ 25 (N=66)	PTA > 25 (N=64)	p-value
Age, years, mean (std)	73.9 (7.0)	79.10 (6.7)	<.0001
Men	16 (24.2)	29 (45.3)	0.01
Best Ear PTA, mean (std)	21.4 (1.9)	34.4 (6.6)	<0.001
Subjective Hearing Difficulty	1 (1.5)	10 (15.6)	<.001
Education years, mean (std)	14.7 (1.9)	15.2 (2.0)	0.14
Ever Smokers	25 (37.9)	28 (43.8)	0.50
Alcohol drinks/day mean (std)	0.6 (0.9)	0.9 (1.0)	0.10
Regularly Exercise	55 (83.3)	46 (71.9)	0.12
Diabetes	6 (9.1)	5 (7.8)	0.79
Hypertension	32 (48.5)	43 (67.2)	0.03
Prevalent CVD	1 (1.5)	5 (7.8)	0.09

Note. PTA: Pure tone average threshold; std: standard deviation; CVD: cardiovascular disease.

Table 2.

Standardized beta estimates of the association of hearing acuity measured in 2003-2005 with diffusion metrics in select brain regions, from MRI data acquired in 2014-2016 from participants of the Rancho Bernardo Study of Healthy Aging.

	Left Hemisphere				Right Hemisphere			
	β	S.E.	95% CI	p	β	S.E.	95% CI	p
Restricted Diffusion								
Transverse Temporal	−0.105	0.100	−0.303 to 0.093	0.298	**−0.216**	0.097	−0.408 to −0.024	0.028
Superior Temporal	−0.102	0.100	−0.301 to 0.096	0.308	−0.169	0.093	−0.354 to 0.015	0.071
Hippocampus	−0.107	0.089	−0.282 to 0.069	0.232	−0.149	0.093	−0.332 to 0.034	0.111
Pars Triangularis	−0.093	0.093	−0.278 to 0.092	0.322	**−0.300**	0.093	−0.484 to −0.115	0.002
Pars Opercularis	−0.068	0.098	−0.261 to 0.126	0.490	**−0.260**	0.100	−0.457 to −0.063	0.010
Middle Frontal	**−0.220**	0.092	−0.402 to −0.038	0.018	**−0.232**	0.095	−0.421 to −0.045	0.016
Anterior Cingulate	−0.135	0.105	−0.343 to 0.073	0.200	−0.196	0.103	−0.399 to 0.008	0.059
Pericalcarine	−0.154	0.095	−0.343 to 0.035	0.109	−0.008	0.091	−0.189 to 0.172	0.930
Free Water								
Transverse Temporal	0.003	0.089	−0.173 to 0.179	0.974	0.170	0.092	−0.013 to 0.352	0.068
Superior Temporal	0.119	0.084	−0.047 to 0.285	0.157	0.103	0.080	−0.055 to 0.262	0.200
Hippocampus	0.167	0.085	−0.002 to 0.335	0.053	**0.210**	0.090	0.031 to 0.388	0.022
Pars Triangularis	0.061	0.088	−0.113 to 0.235	0.489	**0.179**	0.085	0.010 to 0.348	0.038
Pars Opercularis	0.074	0.088	−0.100 to 0.249	0.402	**0.203**	0.084	0.036 to 0.348	0.017
Middle Frontal	0.136	0.086	−0.035 to 0.306	0.118	0.137	0.087	−0.034 to 0.369	0.116
Anterior Cingulate	0.116	0.091	−0.064 to 0.296	0.205	**0.258**	0.091	0.077 to 0.438	0.005
Pericalcarine	0.117	0.092	−0.065 to 0.299	0.204	0.087	0.087	−0.086 to 0.260	0.320

Note. Negative β values indicate that for each standard deviation (SD) increase in hearing thresholds (i.e. 8 dB) restricted diffusion decreased by the shown amount, in SD units). Models adjusted for age, gender, years of education, smoking status, physical activity, alcohol use, hypertension, diabetes, and prevalent CVD. Bolded values reflect estimates for which confidence intervals did not include the null.