Hippocampal atrophy is associated with hearing loss in cognitively normal adults

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Objectives: A growing body of evidence suggests that age-related hearing loss (HL) is associated with morphological changes of the cerebral cortex, but the results have been drawn from a small amount of data in most studies. The aim of this study is to investigate the correlation between HL and gray matter volume (GMV) in a large number of subjects, strictly controlling for an extensive set of possible biases.

Methods: Medical records of 576 subjects who underwent pure tone audiometry, brain magnetic resonance imaging (MRI), and the Korean Mini-Mental State Exam (K-MMSE) were reviewed. Among them, subjects with normal cognitive function and free of central nervous system disorders or coronary artery disease were included. Outliers were excluded after a sample homogeneity check. In the end, 405 subjects were enrolled. Pure tone hearing thresholds were determined at 0.5, 1, 2, and 4 kHz in the better ear. Enrolled subjects were divided into 3 groups according to pure tone average: normal hearing (NH), mild HL (MHL), and moderate-to-severe HL (MSHL) groups. Using voxel-based morphometry, we evaluated GMV changes that may be associated with HL. Sex, age, total intracranial volume, type of MRI scanner, education level, K-MMSE score, smoking status, and presence of hypertension, diabetes mellitus and dyslipidemia were used as covariates.

Results: A statistically significant negative correlation between the hearing thresholds and GMV of the hippocampus was elucidated. Additionally, in group comparisons, the left hippocampal GMV of the MSHL group was significantly smaller than that of the NH and MHL groups.

Conclusion: Based on the negative correlation between hearing thresholds and hippocampal GMV in cognitively normal old adults, the current study indicates that peripheral deafferentation could be a potential contributing factor to hippocampal atrophy.

KEYWORDS

hippocampus, hearing loss, atrophy, aging, structural neuroimaging

1. Introduction

Age-related hearing loss (ARHL) is one of the most common sensory impairments in elderly subjects. ARHL is characterized by difficulties in speech understanding in acoustically adverse settings, delayed central auditory processing, and compromised sound localization (Gates and Mills, 2005). Due to the high prevalence and its impact on everyday life, ARHL is a great social burden. In subjects over 65 years of age, one in three suffer from hearing loss (HL), and in those over 80, HL affects more than a half (Roth et al., 2011; Homans et al., 2017). ARHL is the leading cause of years lived with disability for population over 70 years of age (Collaborators, 2021). Due to population growth and aging, the number of people living with HL is expected to rise by 56.1%, from 1.57 billion in 2019 to 2.45 billion in 2050 (Collaborators, 2021). Therefore, the social burden of ARHL is expected to rise continuously.

In addition to the high prevalence of presbycusis, ARHL has received considerable attention associated with cognitive decline. An expanding array of research indicates a correlation between ARHL and both cognitive deterioration and an increased risk for dementia (Lin et al., 2011, 2013; Deal et al., 2017). Furthermore, the Lancet Commission on Dementia Prevention identified ARHL as the most significant modifiable risk factor for dementia (Livingston et al., 2017).

Although the relationship between ARHL and cognitive decline has been confirmed in many epidemiological studies, how the two are linked remains unclear. Recently, many studies have attempted to elucidate the mechanism, including through analysis of brain imaging data. Structural imaging studies have been conducted to identify the association between HL and brain volumes of auditory- and non-auditory regions of the brain. However, there are stark disparities among studies. The auditory cortex has been the most frequently investigated region, but even the volumetric changes in the auditory cortex have shown inconsistent results among studies (Lin et al., 2014; Giroud et al., 2017; Rigters et al., 2017; Ren et al., 2018; Eckert et al., 2019). Also, other studies have evaluated the association between HL and a more extensive set of regions known to support auditory perception, such as the cingulate cortex, amygdala, and hippocampus, but the relationship between HL and cortical reorganization has not been fully elucidated yet (Uchida et al., 2018; Armstrong et al., 2019; Belkhiria et al., 2019, 2020).

In this regard, we sought to investigate the correlation between volumetric changes of the cerebral cortex and ARHL using whole-brain exploratory analysis in a large series of subjects. Also, by controlling numerous variables that can affect brain volume, the HL-related changes in the cerebral cortex in the current study were minimally biased by other factors.

2. Materials and methods

2.1. Subjects

This is a single-center retrospective cohort study. We retrospectively reviewed subjects who visited Seoul National University Hospital Healthcare System Gangnam Center from January 2017 to June 2020. A total of 576 adults who were older than 50 years and had undergone pure tone audiometry, brain magnetic

resonance imaging (MRI), and the Korean Mini-Mental State Exam (K-MMSE) were initially screened. Subjects with cognitive decline (K-MMSE score < 24) ($n = 101$), central nervous system (CNS) disorders ($n = 13$), coronary artery disease (CAD) requiring percutaneous coronary intervention or coronary artery bypass grafting ($n = 51$) were excluded from the study, along with outliers from a voxel-based morphometry (VBM) sample homogeneity test ($n = 10$) (Kang et al., 1997). Four subjects had both CNS disorder and CAD. As a result, 405 eligible subjects were finally enrolled in this study. The pure tone audiometric thresholds were calculated by averaging thresholds at 0.5, 1, 2, and 4 kHz of the better ear. Enrolled subjects were divided into three groups according to pure tone average based on the WHO's grades of hearing impairment: normal hearing (NH, <25 dB), mild hearing loss (MHL, ≥25 dB and <40 dB), and moderate-to-severe hearing loss (MSHL, ≥40 dB) (World Health Organization, 1991). The study was approved by the Institutional Review Board of the Clinical Research Institute at Seoul National University Hospital (IRB No. 2009-011-1154).

2.2. Image acquisition

The subjects underwent brain structural MRI using one of three types of scanner: 1.5 T brain MRI (i) Achieva (179 subjects; Philips Medical Systems, Best, The Netherlands), (ii) MAGNETOM Espree (105 subjects; Siemens, Erlangen, Germany) or 3 T brain MRI (iii) MAGNETOM Skyra (121 subjects; Siemens, Erlangen, Germany). Structural images were acquired with (i) 3D T1 weighted TFE sequence with repetition time (TR) = 7.5 ms, echo time (TE) = 3.4 s, flip angle (FA) = 8°, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3, slice thickness = 1 mm, 160 sagittal slices, field of view (FOV) = 240 mm, (ii) 3D T1 weighted TFL sequence with TR = 1,020 ms, TE = 4.29 s, FA = 15°, voxel size = $0.9 \times 0.9 \times 1.0$ mm^3, slice thickness = 1 mm, 160 sagittal slices, FOV = 240 mm, or (iii) 3D T1 weighted MPRAGE sequence with TR = 1,600 ms, TE = 2.84 s, FA = 9°, voxel size = $0.5 \times 0.5 \times 1.0$ mm^3, slice thickness = 1 mm, 192 sagittal slices, FOV = 240 mm.

2.3. Preprocessing of MRI images for VBM analysis

VBM analysis of the T1-weighted images was performed using the Computational Anatomy Toolbox (CAT12[1]) implemented in Statistical Parametric Mapping 12 (SPM12[2]) software using MATLAB (R2020b). For pre-processing, default settings according to the standard protocol were used. All scans were segmented into gray matter (GM), white matter, and cerebrospinal fluid and spatially normalized to Montreal Neurological Institute (MNI) stereotactic space using DARTEL (diffeomorphic anatomical registration through an exponentiated Lie algebra) algorithm. Then, normalized GM images were modulated (i.e., scaled by the amount of expansions and contractions that has occured during spatial normalization), so that voxel-wise gray matter volumes (GMV) remains the same as in

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1 http://www.neuro.uni-jena.de/cat/

2 http://www.fil.ion.ucl.ac.uk/spm/

TABLE 1 Clinical and demographic characteristics of the three groups.

	Normal (*n* = 242)	Mild HL (*n* = 91)	Mod to severe HL (*n* = 72)	*p*-value
Age, mean (SD), years	65.09 (6.92)	70.79 (6.93)	73 (6.81)	<0.001*
Sex, *n* (%)				0.091
Male	96 (39.7)	38 (41.8)	39 (54.2)	
Female	146 (60.3)	53 (58.2)	33 (45.8)	
TIV, mean (SD), cm^3	1433.20 (144.05)	1437.93 (140.52)	1446.26 (145.24)	0.620
Education, mean (SD), years	14.15 (2.74)	14.02 (3.57)	13.73 (3.52)	0.778
MMSE, mean (SD)	27.22 (2.40)	26.64 (1.69)	26.45 (1.84)	<0.001*
PTA, mean (SD), dB	16.85 (4.79)	31.19 (4.19)	49.89 (9.17)	<0.001*
Hypertension, *n* (%)	84 (34.7)	41 (45.1)	39 (54.2)	<0.008*
Diabetes Mellitus, *n* (%)	39 (16.1)	17 (18.7)	21 (29.2)	<0.047*
Dyslipidemia, *n* (%)	111 (45.9)	50 (54.9)	36 (50.0)	0.326
Smoking, *n* (%)				0.131
Never-smoker	189 (78.1)	72 (79.1)	49 (68.1)	
Ex-smoker	17 (7.0)	7 (7.7)	5 (6.9)	
Current-smoker	36 (14.9)	12 (13.2)	18 (25)	

Mod, moderate; HL, hearing loss; SD, standard deviation; n, number; TIV, total intracranial volume; MMSE, mini-mental state examination; PTA, pure tone audiometry.

individual native space. After segmentation, a quality check was conducted. The normalized segmented images were smoothed using an 8-mm FWMH Gaussian kernel. We used an absolute masking threshold of 0.1.

2.4. Statistical analysis

Multiple regression analysis was performed to evaluate correlations between hearing thresholds and GMV. Sex, age, total intracranial volume (TIV), type of MRI scanner, education level, MMSE score, hypertension, diabetes mellitus, dyslipidemia, and smoking status were used as covariates to minimize bias while evaluating correlations between hearing thresholds and GMV. The differences in GMV between the three groups were evaluated with factorial analysis with the type of MRI scanner and group according to PTA as factors. By analyzing the data in this way, inter-scanner differences were adjusted for as described in previous literature (Pardoe et al., 2008). Again, sex, age, TIV, education level, MMSE score, hypertension, diabetes mellitus, dyslipidemia, and smoking status were used as covariates. The *post-hoc* test was performed using the Mann–Whitney U test with Bonferroni correction. All results were corrected for multiple comparisons to a significant level of voxel-level *p* < 0.05, family-wise error (FWE)-corrected, and a cluster size >10 voxels was adopted. Because all continuous clinical and demographic data (better ear hearing level, TIV, and MMSE) were not normally distributed (confirmed by the Shapiro-Wilks test, *p* < 0.05 for all continuous parameters), we compared the three groups using the Kruskal-Wallis test for the continuous data and the χ^2-test for the categorical data. All statistical analyses were performed with the SPSS 23 (IBM Corporation, New York, USA) package using a two-sided test with a significance level of 0.05.

2.5. Covariates

In statistical analysis, 10 covariates (sex, age, TIV, type of MRI scanner, education level, K-MMSE score, hypertension, diabetes mellitus, dyslipidemia, and smoking status) were adjusted. Variables that could potentially be confounders in the relationship between hearing thresholds and brain volume, and variables known to be associated with HL were used as covariates. Smoking status was based on self-report. The diagnosis of hypertension, diabetes mellitus, and dyslipidemia was established based on a history of a physician diagnosis, pharmacologic treatment, and self-report.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of 405 subjects are summarized in Table 1. Two hundred and forty-two subjects with a PTA < 25 dB were classified as the NH group, 91 subjects with a PTA ≥ 25 dB and < 40 dB were classified as the MHL group, and 72 subjects with a PTA ≥ 40 dB were classified as the MSHL group. There were no significant differences between the three groups with regard to sex, TIV, education level, dyslipidemia, and smoking status. The age of the NH group was significantly lower than that of the MHL and the MSHL groups. The K-MMSE score of the NH group was significantly higher than that of the MHL and the MSHL groups. The prevalence of hypertension and diabetes was higher in the MSHL group than in the NH group.
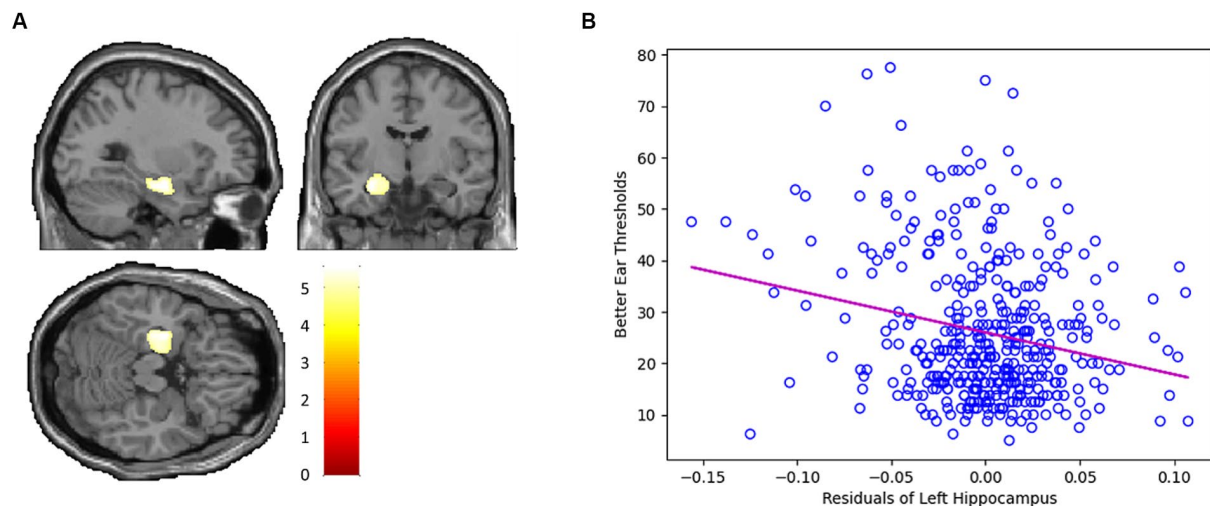
FIGURE 1
(A) Whole-brain voxel-level linear correlation analysis indicates that the volume of the left hippocampus (peak MNI x, y, z coordinates = −29, −9, −18; peak z-value = 5.43) is negatively associated with hearing threshold. **(B)** Scatter plot depicting the negative linear correlation between the GMV of the left hippocampus and hearing threshold.
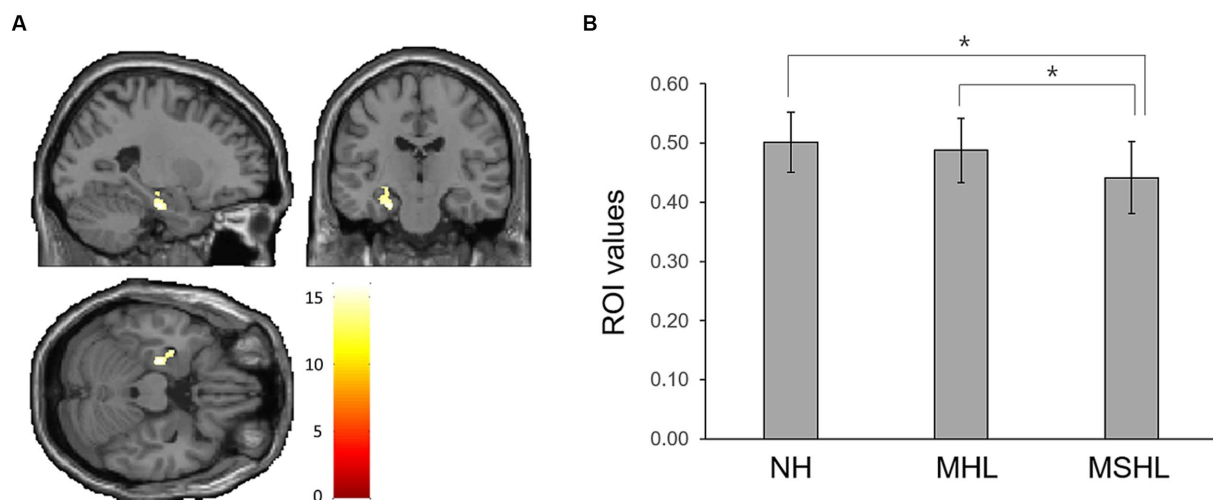

FIGURE 2
(A) The left hippocampus (peak MNI x, y, z coordinates = −24, −18, −23; peak z-value = 5.06) showed a significant difference between the groups.
(B) On *post-hoc* analysis, the moderate to severe hearing loss group showed significantly decreased left hippocampal volume compared to that of the mild hearing loss (MHL) ($p < 0.001$) and the normal hearing (NH) groups ($p < 0.001$). There were no significant differences between the MHL group and the NH group. Asterisks (*) indicate a statistically significant difference with a p-value of less than 0.05.

3.2. Correlation analyses between GMV and HL

Whole-brain voxel-level linear correlation analyses revealed that the volume of the left hippocampus (peak MNI x, y, z coordinates = −29, −9, −18; peak z-value = 5.43) was negatively associated with hearing threshold (Figure 1).

3.3. Group comparison of GMV

The factorial analysis found that the left hippocampus (peak MNI x, y, z coordinates = −24, −18, −23; peak z-value = 5.06) showed a significant difference between the groups (Figure 2A). On *post-hoc* analysis, the MSHL group showed significantly decreased left hippocampal volume compared to that of the MHL ($p < 0.001$) and the NH groups ($p < 0.001$). There were no significant differences between the MHL group and the NH group (Figure 2B).

4. Discussion

While evidence suggests that peripheral HL is associated with accelerated cognitive decline and elevated dementia risk (Lin et al., 2011, 2013; Deal et al., 2017) the underlying mechanism remains unclear. As part of elucidating this mechanism, the present study

observed an inverse relationship between hearing thresholds and hippocampal GMV, a structure critically involved in dementia development, even among subjects with normal cognitive function.

Consistent with our study, two recent investigations, including a cohort study, have reported associations between HL and diminished hippocampal volume as well as accelerated volume decline (Uchida et al., 2018; Armstrong et al., 2019). Moreover, hippocampal atrophy is an indicator of neurodegeneration, as a proxy of neuronal loss, and is closely tied to accelerated volume reduction in both adults experiencing cognitive decline and those diagnosed with Alzheimer's Disease (AD) (Jack et al., 2002; de Leon et al., 2004; Shi et al., 2009; Del Sole et al., 2016). Importantly, hippocampal atrophy may occur even before the onset of clinical AD symptoms (Lewczuk et al., 2015; McConathy and Sheline, 2015). Given these considerations, it is plausible that the effect of HL on cognitive decline might be mediated through changes in the hippocampus.

The hippocampus plays a multifaceted role in information processing and memory, with the right hippocampus generally implicated in spatial navigation and visual memory, while the left hippocampus predominantly engages in perception, learning and recall of speech (Ezzati et al., 2016; Billig et al., 2022). Our results specifically implicate the left hippocampus, consistent with its known lateralization. The hippocampus certainly receives and operates on auditory information (for a review, see Billig et al., 2022), and its pyramidal place cells (O'Keefe and Dostrovsky, 1971) can map out dimensions of sound as they do for space, at least in rodents (Aronov et al., 2017). The hippocampus is also active during auditory working memory (Bishop and Miller, 2009; Davis et al., 2011; Kumar et al., 2016; Lad et al., 2020; Kumar et al., 2021) and may provide predictive information to superior temporal sites during continuous speech listening (Michelmann et al., 2021). Given the challenges in speech recognition under acoustically challenging conditions associated with ARHL (Tun et al., 2002; Best et al., 2010), coupled with the left hippocampal functions, it could be hypothesized that the cognitive load on the left hippocampus may be elevated in individuals with ARHL. It has been suggested that excessive activation of hippocampal neurons could lead to hippocampal degeneration and a worsening of AD pathology (de Haan et al., 2012; Beckmann et al., 2020). In this context, Griffiths et al. emphasized the possibility of a bidirectional relationship between medial temporal lobe dysfunction and HL, which could interact with AD pathology (Griffiths et al., 2020). Such a relationship is suggested to be mediated by the decline in spectral and temporal resolution in ARHL that complicates speech-in-noise analysis, thereby necessitating heightened hippocampal activity (Gordon-Salant et al., 2007; Pichora-Fuller et al., 2007). This theory might explain the findings of the present study and the previous two studies (de Haan et al., 2012; Beckmann et al., 2020).

Alternatively, impaired adult hippocampal neurogenesis (AHN) could serve as an explanatory factor for the inverse association between hearing thresholds and hippocampal GMV. The hippocampus is one of the few areas of the brain where neurogenesis persists even during adulthood (Ernst and Frisen, 2015). Recent literature suggests that compromised AHN may contribute to hippocampal atrophy (Anand and Dhikav, 2012; Schloesser et al., 2014; Schoenfeld et al., 2017). Compromised AHN is observed in the early stages of AD, even before clinical symptoms and amyloid deposition occur (Lazarov and Hollands, 2016; Liu et al., 2021). Multiple AD pathology-related factors, including tau protein and Aβ, among others, disturb AHN and

exacerbate cognitive deficits (Mu and Gage, 2011; Hollands et al., 2017; Liu et al., 2021). In animal studies, noise-induced hearing loss (NIHL) has been shown to decrease AHN and impair memory (Kraus et al., 2010; Liu et al., 2016; Shukla et al., 2019), with these effects persisting up to 12 months after noise exposure evidenced by increased hippocampal tau-phosphorylation, which may inhibit AHN (Pristera et al., 2013; Komuro et al., 2015; Park et al., 2018; Houben et al., 2019). Since NIHL is a prominent type of acquired HL and shares pathophysiological mechanisms with ARHL, the findings from NIHL studies could be applied to ARHL (Yang et al., 2015; Hederstierna and Rosenhall, 2016; Liberman, 2017). Notably, the cited animal studies propose that HL, rather than noise trauma *per se*, modulates neurogenesis (Liu et al., 2016; Shukla et al., 2019). This assertion is further corroborated by a study using a conductive hearing loss (CHL) mouse model, which also demonstrated a reduction in AHN following CHL (Kurioka et al., 2021). Recent evidence indicates that neurogenesis-related pathways including cellular differentiation and morphogenesis during development, among others, are associated with hippocampal atrophy (Horgusluoglu-Moloch et al., 2019). Accordingly, the resultant smaller hippocampal volume could be a consequence of HL-modulated AHN. In addition, various factors such as environmental enrichment, exercise, stress, and social isolation affect AHN (Gould et al., 1997; Kempermann et al., 1997; Lemaire et al., 2000; van Praag et al., 2000; Kreisel et al., 2014; Voss et al., 2019), suggesting that HL-induced stress and social isolation could indirectly contribute to AHN and hippocampal atrophy.

In the group comparison of our study, the left hippocampal GMV of the MSHL group was smaller than that of the NH and MHL groups. The MHL group showed no significant difference from the NH group in hippocampal volume. The risk of incident dementia is increased more steeply with moderate to severe HL (Lin et al., 2011; Deal et al., 2017). Moderate to severe HL seems to have a more significant effect on hippocampal atrophy and cognitive function deterioration. Hearing aid use slows the decline of episodic memory, one of the functions of the left hippocampus (Maharani et al., 2018). Early intervention before moderate HL occurs might help prevent the progression of cognitive impairment. Additional research is required to assess the impact of early intervention on cognitive outcomes.

Studies on the association between HL and structural changes of the auditory cortex showed inconsistent results. Our results did not show any correlation between GMV of the auditory cortex and hearing thresholds. This aligns with prior research indicating that the effect of ARHL on the auditory cortex is minimal, while the process of aging exerts a substantial impact (Profant et al., 2013, 2014; Ouda et al., 2015; Profant et al., 2015, 2020). Conversely, some studies have shown a correlation between peripheral HL and GM atrophy in the primary auditory cortex (Peelle et al., 2011; Eckert et al., 2012; Lin et al., 2014; Ren et al., 2018; Uchida et al., 2018). ARHL is a term with a broad scope, and there are various subgroups within it according to the type or etiology of HL. The inclusion in these studies of patients with various types of HL without distinction might result in these inconsistent results.

There are some limitations in our study design. First, since this is a cross-sectional study, while a relationship between HL and hippocampus atrophy is revealed, a causal link between the two is yet to be unveiled. However, while the results are correlational, and therefore do not directly demonstrate a causal relationship, we believe that the best interpretation is that hippocampal atrophy is a

consequence of moderate-to-severe HL; this would be consistent with existing evidence for HL causing impaired neurogenesis in hippocampus, as its eventual consequence, though could be the result of alternative structure–function relationships. Second, MRI obtained using scanners of different field strengths were included in this study. In case of a consistent bias, it might be viable to adjust the scanner type to enhance cross-site comparability. In our study, the scanner type was adjusted as a covariate in correlation analysis. In addition, to check the reliability of these results, a comparison between groups was performed using factorial analysis, as introduced by Pardoe et al. to correct inter-scanner differences in multi-site studies (Pardoe et al., 2008). The factorial analysis also confirmed the association between HL and hippocampus atrophy.

The strengths of our study lie in its rigorous design and the use of a large sample size ($n = 405$). A key advantage is our meticulous approach to address potential biases and confounding factors. By carefully controlling for covariates such as age, sex, total intracranial volume, education level, cognitive status, hypertension, diabetes mellitus, dyslipidemia, and smoking status in our statistical analysis, we ensure robustness and validity of our findings. The substantial sample size further enhanced the study's statistical power, allowing for a comprehensive and reliable investigation of the association between HL and brain structure, leading to more meaningful conclusions.

5. Conclusion

This study demonstrates a negative correlation between hearing thresholds and hippocampal GMV in cognitively normal old adults. This result suggested that peripheral deafferentation could be a potential contributing factor to hippocampal atrophy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of the Clinical Research Institute at Seoul National University Hospital (IRB No. 2009-011-1154). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YS: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. WJ: Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AB: Investigation, Writing – review & editing. WS: Investigation, Writing – review & editing. J-JS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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