



OPEN Atrophy of cerebellum Crus I indicates poor outcome of cochlear implantation in the elderly

Jun Yup Kim¹, Dongyeop Kim², Juchan Jung², Beomseok Sohn³, Kyung Min Kim⁴,
Jae Young Choi⁵ & Seong Hoon Bae⁵✉

Cochlear implantation (CI) is a highly effective treatment for profound hearing loss in elderly individuals, including those with ARHL. However, factors influencing the success of CI in the elderly population are not fully understood. Hence, we sought to investigate the association of regional cerebellar gray matter volume with effectiveness of CI in the elderly. This retrospective cross-sectional study included CI implantees and healthy controls aged ≥ 70 years. We used voxel-based morphometry to investigate the cerebellar gray matter associated with speech perception outcome in the CI group. Among the study participants, cerebellar gray matter volume loss, particularly in the Crus I region, was associated with poorer CI outcomes. Notably, this association was stronger than that observed for the duration of hearing deprivation (DoD). Moreover, the degree of cerebellar atrophy and DoD were found to be independent of each other. No significant correlation was found between the age of the implant and CI outcomes. The findings suggest that cerebellar gray matter atrophy, specifically in the Crus I region, may serve as a predictor of poor outcomes following cochlear implantation in elderly individuals. These results underscore the importance of assessing cerebellar volume loss alongside other factors when counseling elderly patients considering CI.

Keywords Cerebellum, Elderly hearing loss, Speech perception, Cochlear implantation, Voxel-based morphometry

Abbreviations

Pre	The preoperative scores
Post	The postoperative scores
MSW	Monosyllabic word test
DSW	Disyllabic word test
SPT	Sentence perception test
DoD	Duration of hearing deprivation
MNI	Montreal Neurological Institute
ROI	Region of interest
TFCE	Threshold-free cluster enhancement

As human life expectancy increases, the incidence of age-related hearing loss (ARHL) also increases, affecting 70–80% of people over the age of 75 and over 300 million people worldwide¹. Hearing loss (HL) has a significant adverse impact on quality of life and is reported as a risk factor for depression and dementia in the elderly^{2,3}. Cochlear implantation (CI) is the most effective treatment for profound HL in the elderly from a variety of causes, including ARHL^{4,5}. Several factors have been proposed to influence the prognosis of CI in the elderly, such as implant age, etiology of hearing loss, and preoperative cognitive-language function^{6,7}. Of these, the patient-reported duration of hearing deprivation (DoD) is one of the most important factors, although it has a vague definition and is collected by subjective survey^{8,9}.

With the development of functional imaging and image analysis techniques, the brain area related to hearing perception has been deeply investigated. The cerebral cortices, including the auditory pathway, have been

¹Department of Physical Medicine and Rehabilitation, Hanyang University Medical Center, Seoul, Republic of Korea.

²Department of Education and Training, Severance Hospital, Seoul, Republic of Korea. ³Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. ⁴Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea. ⁵Department of Otorhinolaryngology, Yonsei University College of Medicine, 50, Yonsei-Ro, Seodaemun-Gu, Seoul 03722, Republic of Korea. ✉email: bshsap@naver.com

focused on, revealing significant differences between the hearing loss and normal hearing groups¹⁰. In contrast, the cerebellum has received less attention, as it is traditionally believed to be related to motor function, cognitive function, affect regulation, and motor speech^{11,12}. However, some animal and human studies have indicated that the cerebellum is also related to semantic perception, although it does not directly deprive hearing function when lesioned¹³. A recent study using resting-state functional magnetic resonance imaging (MRI) suggested that the cerebro-cerebellar and cerebellar subregional connectivity could be weakened in the presence of sensorineural hearing loss compared with healthy controls¹⁴. Furthermore, the relevance of the right cerebellum to speech perception has been reproduced through various event-related functional MRI (fMRI) studies of healthy volunteers^{15,16}. According to a multisite study published by the Alzheimer's Disease Neuroimaging Initiative, patients with Alzheimer's disease who complained of hearing loss had significantly smaller cerebellar white matter and gray matter volumes than those who did not¹⁷. With these prior studies enabling speculation about the correlation between the cerebellum and speech perception, we hypothesized that the preoperative regional gray matter volume of the cerebellum can predict the effectiveness of CI in the elderly.

Across a variety of methodologies including voxel-based morphometry (VBM), diffusion tensor imaging, and post-mortem brain study, changes in the cerebellum with aging have been reported uniformly, with smaller cerebellum volumes and reduced white matter integrity in the elderly¹⁸. Although in sensorineural hearing loss, as mentioned above, a weakening of functional connectivity centered in the cerebellum has been reported, there has been no report on structural changes in the cerebellum. If a relationship is found between regional gray matter volume reduction in the cerebellum and the effects of CI, the cerebellum may become another biomarker for prognosis after CI. Hence, this study aimed to investigate the association of regional cerebellar gray matter volume with effectiveness of CI in the elderly. Voxel-based morphometry (VBM) was applied to MRI of the temporal lobe (tMRI) which is frequently used MR sequence for pre-operative evaluation before CI. We analyzed the effect of cerebellum gray matter volume on the outcomes of CI and compared it with that of other factors. To confirm the results, age- and sex-matched healthy controls who underwent MRI for regular health check-ups were compared.

Results

Demographic data and factors associated with CI outcomes

Among the 147 candidates who underwent CI at the age of 70 years or older, a total of 52 subjects (mean age $\pm$ SD, 75.5 ± 4.2 years; 32 females [61.5%]) met the inclusion criteria and were ultimately included in the CI group. The control group comprised 52 subjects (mean age $\pm$ SD, 76.1 ± 3.6 years; 33 females [63.5%]), matched by sex and age at brain MRI with the CI group (Table 1). Comparative analysis revealed no significant differences in demographic characteristics, including sex and age at MRI, between the CI group and the other two groups. Within the CI group, the most prevalent etiology of hearing loss was reported as ARHL (55.8%), followed by chronic otitis media, sudden sensorineural hearing loss, otosclerosis, and otosyphilis.

Correlation analysis between variables was conducted to identify positive or negative relationships, particularly the effects of DoD and age on CI outcomes. (Fig. 1) Among the observed correlations, the outcomes of CI, specifically the postoperative scores of SIT, exhibited relatively weak positive correlations with the pre-implantation scores. Strong positive correlations were found between pre- and post-speech intelligibility test subtests (SPT, MSW, and DSW). Furthermore, DoD demonstrated significant negative correlations with all CI outcomes, which aligned with the findings from prior studies. Surgical side pure tone audiometry (PTA) and contralateral side PTA were not related with the outcomes of CI. Age and DoD were positively correlated, possibly explained by the higher proportion of ARHL patients. Interestingly, age at CI was not significantly associated with any of the CI outcomes.

Gray matter volume and CI outcomes

The study-specific cerebellar gray matter ROI was composed of 4149 voxels (Figure S1 and Table S1). Among them, 2095 (50.5%) voxels belonged to the bilateral Crus I. In VBM using the GLM adjusted for default regressors with DoD as the regressor of interest, no voxel survived the statistical threshold (peak TFCE Z-value = 9.5, threshold Z-value = 10.2). This implies that cerebellum gray matter volume is not correlated with DoD.

GLM-based regression analyses were employed to investigate the association between scores for each subitem of the SIT and cerebellar gray matter voxel-wise intensity. Notably, only five subitems exhibited statistically significant clusters (Table 2 and Fig. 2). Specifically, for PostSPT and PostMSW, over half of the surviving voxels were attributed to the right Crus I, whereas for PreSPT, PreMSW, and PreDSW, the majority of voxels were associated with the left Crus I. This suggests that CI outcomes are linked to the right Crus I, while preoperative speech intelligibility is correlated with the left Crus I. Moreover, the volume of the right Crus I gray matter displayed stronger correlations with the five significant subitems compared to DoD (Table 3).

To validate these findings, a specificity analysis was conducted using surgical laterality and preoperative contralateral PTA, which are less likely to be associated with CI outcomes or speech intelligibility. As anticipated, no voxel survived the statistical threshold, indicating the absence of significant associations (peak TFCE Z-values for surgical laterality right > left, left > right, and contralateral PTA = 9.9, -8.9, and -3.3, respectively; TFCE Z-value thresholds = 10.8, -10.1, and -10.2, respectively). Furthermore, a comparison of voxel-wise intensity between the control group and the CI group corroborated the relationship between the left Crus I and hearing function, as the control group exhibited significantly higher voxel-wise intensity in bilateral Crus I and VI (Table 2 and Fig. 3).

Characteristics	CI (n = 52)	HC (n = 52)	Test statistic, <i>P</i>
Age at CI, mean (SD), y	75.5 (4.2)	76.1 (3.6)	<i>T</i> = 0.70, <i>P</i> = 0.44
Sex, No. (%)			
Male	20 (38.5)	19 (36.5)	$\chi^2 = 0.04$, <i>P</i> = 0.84
Female	32 (61.5)	33 (63.5)	
Medical history, No. (%)			
Hypertension	28 (53.8)	29 (55.8)	$\chi^2 = 0.04$, <i>P</i> = 0.84
Diabetes	8 (15.4)	18 (34.6)	$\chi^2 = 5.12$, <i>P</i> = 0.02
Smoking history			
Non-smoker	45 (86.5)	46 (88.5)	<i>Z</i> = 0.24, <i>P</i> = 0.81
Ex-smoker	6 (11.5)	5 (9.6)	
Current smoker	1 (1.9)	1 (1.9)	
Cardiovascular disease	7 (13.5)	10 (19.2)	$\chi^2 = 0.63$, <i>P</i> = 0.43
Duration of hearing deprivation (SD), y	8.5 (8.8)		
Etiologies of hearing loss, No. (%)		NA	
Chronic otitis media	16 (30.8)		
Sudden sensorineural hearing loss	5 (9.6)		
Otosclerosis	1 (1.9)		
Otosyphilis	1 (1.9)		
Age-related hearing loss	29 (55.8)		
Laterality of CI surgery, No. (%)			
Right	33 (63.5)		
Left	19 (36.5)		
Preoperative PTA4, mean (SD), dB			
CI side	92.3 (17.2)		
contralateral side	84.1 (15.3)		
Preoperative SIT scores, mean (SD), %			
MSW	7.3 (12.4)		
DSW	5.8 (12.4)		
SPT	9.8 (16.0)		
Postoperative SIT scores, mean (SD), %			
MSW	46.0 (18.7)		
DSW	51.0 (23.2)		
SPT	64.8 (26.0)		

Table 1. Demographic and clinical characteristics of the CI and control groups. CI, cochlear implantation; DSW, disyllabic word test; HC, healthy control; MSW, monosyllabic word test; NA, not applicable; PTA4, mean dB of pure-tone threshold at frequencies of 500, 1000, 2000, and 3000 Hz pure tone audiometry; SIT, speech intelligibility test in the sound field; SPT, sentence perception test in the sound field.

Discussion

We found that loss of gray matter volume in cerebellum Crus I related with poor CI outcomes. Although DoD showed a significant negative correlation, cerebellum gray matter volume showed a stronger correlation than DoD for CI outcomes. Compared with age- and sex-matched control, elderly patients with HL also showed relatively decreased gray matter volume in the bilateral Crus I and VI. This study sheds light on the possibility that the cerebellum also plays a role in the auditory pathway, which has traditionally been believed to include the brainstem, midbrain, and cerebral cortex rather than the cerebellum.

The mechanism of the relationship between hearing and cerebellar volume may be elucidated by several speculations. First, the cerebrum and cerebellum are connected via the cortico-ponto-cerebellar and cerebello-thalamo-cortical loops¹⁹. When the cerebral cortex is insulted, adverse effects such as hypoperfusion, hypometabolism, and atrophy due to reduced excitatory input and altered hemodynamic condition often occur in the reciprocally connected cerebellum (i.e., crossed cerebellar diaschisis)^{20,21}. A meta-analysis of fMRI studies demonstrated that the auditory cortex and bilateral Crus I were consistently coactivated across studies, regardless of the type of auditory stimuli involved¹³. From this perspective, individuals in the CI group in our study may have experienced a sustained decrease in excitatory inputs to the auditory cortex associated with speech perception. This reduction could lead to atrophy of the cerebral auditory cortex and the cerebellum Crus I, which may be interconnected.

As another speculation, the relationship between CI outcomes and cerebellum volume may also be explained by the direct involvement of the cerebellum in auditory perception. cerebellum Crus I has been reported to be related to dysfunction of both written language perception and auditory language perception when lesioned^{22–26}.

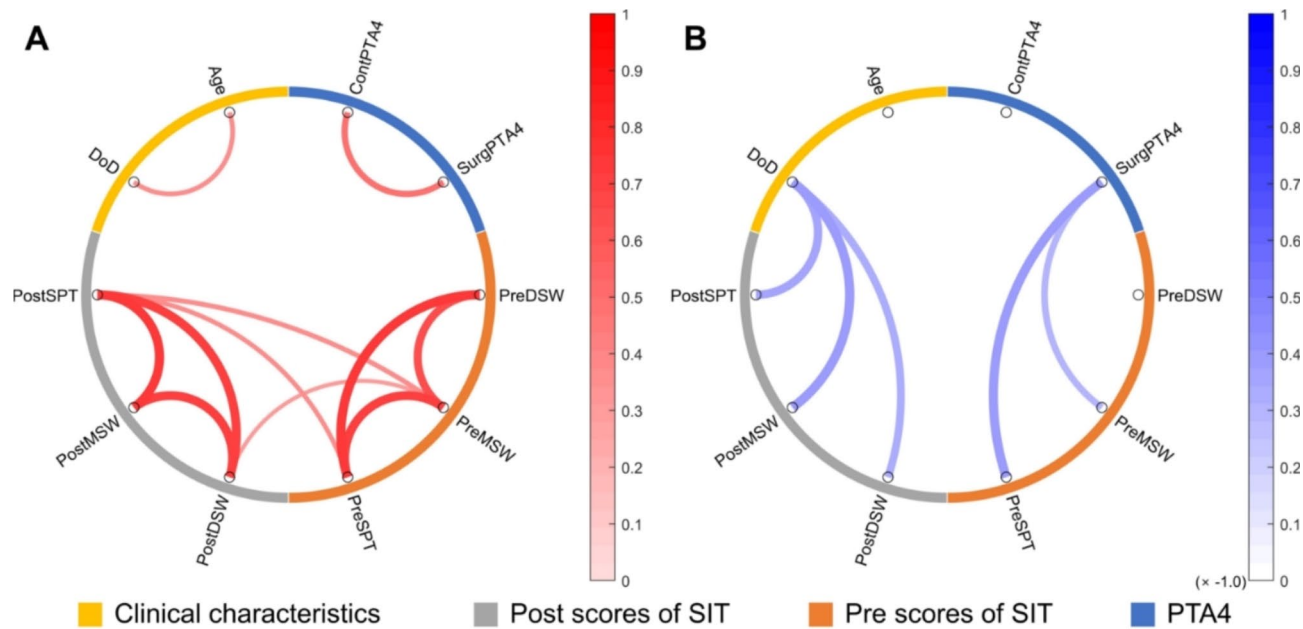


Fig. 1. Circular graphs (A, B) showing inter-variable unadjusted Spearman correlations and distribution of variables in the CI group. Unadjusted Spearman correlation analyses were performed with two-tailed P threshold of 0.05. The color bars on the circular graph and the numbers on the matrix plot show Spearman's rho. (A) Red curves indicate statistically significant positive correlations. (B) Blue curves indicate statistically significant negative correlations. (A, B) Line thickness is proportional to Spearman's rho; Cont, contralateral side of CI; DoD, patient-reported duration of hearing deprivation; DSW, disyllabic word test; MSW, monosyllabic word test; Pre, preoperative; Post, postoperative; PTA4, mean dB of pure tone threshold at frequencies of 500, 1000, 2000, and 3000 Hz pure tone audiometry; SPT, sentence perception test; Surg, surgical side of CI.

	MNI coordinates with peak raw Z					Number of significant voxels and composition ^a					
	SUIT Label	Peak Z	x	y	z	No. of voxels, n	L Crus I, %	R Crus I, %	Vm VIIla, %	L VI, %	R VI, %
Subitem of SIT in the CI group											
PostSPT	R Crus I	3.6	42	−54	−34	158	–	95.6–	–	–	–
PostMSW	R Crus I	3.2	44	−64	−34	36	–	55.6–	41.7	–	–
PreSPT	L Crus I	4.0	−25	−82	−30	184	100.0	–	–	–	–
PreMSW	L Crus I	3.3	−26	−82	−30	150	78.7	21.3	–	–	–
PreDSW	L Crus I	3.4	−26	−82	−32	189	100.0	–	–	–	–
HC group compared with the CI group											
HC	L Crus I	7.9	−34	−60	−30	769	17.0	12.4	–	18.5	18.7

Table 2. Regional distribution of significant cerebellar gray matter voxels according to SIT subitems and comparison groups. CI, cochlear implantation; DSW, disyllabic word test; HC, healthy control; L, left; MNI, Montreal Neurological Institute; MSW, monosyllabic word test; NLH, normal hearing; Pre, preoperative; Post, postoperative; R, right; SIT, speech intelligibility test; SPT, sentence perception test; SUIT, spatially unbiased atlas template of the human cerebellum; Vm, vermis. ^aOnly compositions that account for or more than 10% of surviving voxels for each subitem are shown.

Especially the right Crus I, an area of the cerebellum that is hemodynamically activated during auditory language perception in healthy adults^{15,16}. It is suggested that the cerebellum is responsible for the temporal calculation of phoneme duration and ultimately leads to phoneme discrimination^{15,27}. Collectively, the preserved gray matter volume of the cerebellum Crus I region likely determines the speech intelligibility after CI. In order to find out whether the impact of Crus I on hearing is significant even in normal hearing people, additional research using scored language ability and brain MRI data in normal people will be needed in the future. In addition, the relationship between pre-SIT scores and the left Crus I should be interpreted with caution due to the limited range of preoperative scores, which are generally low. As shown in Table 2, preoperative scores do not exceed 10, which could result in a floor effect. The involvement of bilateral Crus I in hearing seems more reliable, as shown in Fig. 3, which presents the analysis between the HC and CI groups.

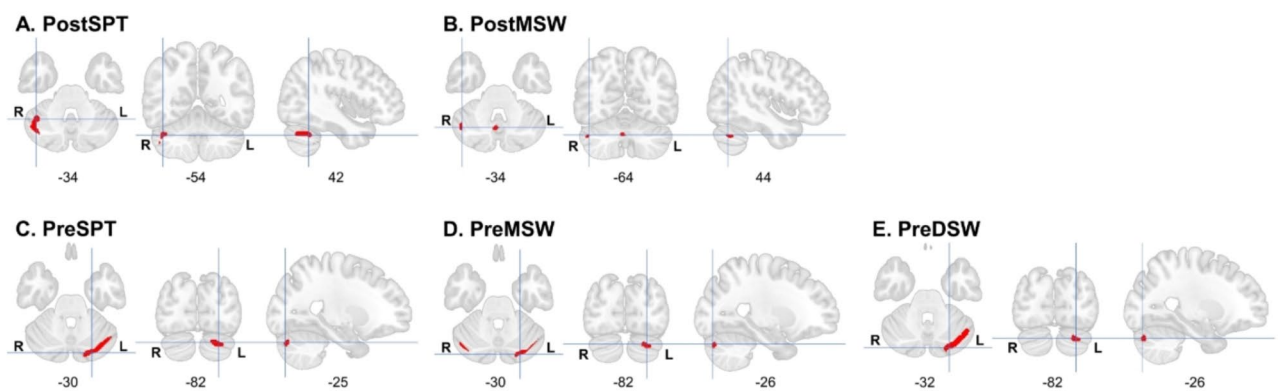


Fig. 2. Binary maps of significant voxels correlated with each speech intelligibility test subitem in voxel-based mapping analyses. Voxel-based mapping analyses were performed with one-tailed P_{FWE} threshold of 0.05, adjusted for age, sex, total intracranial volume, and patient-reported duration of hearing deprivation. Crosshairs indicate the coordinate with the peak raw Z-value for each speech intelligibility test subitem. The MNI-152 coordinates in each row under each slice are, from left to right, z (axial), y (coronal), and x (sagittal). DSW, disyllabic word test; L, left; MNI, Montreal Neurological Institute; MSW, monosyllabic word test; Pre, preoperative; Post, postoperative; R, right; SIT, speech intelligibility test; SPT, sentence perception test.

	MVI		DoD	
	rho	P	rho	P
PostSPT	0.511	<0.001 ^a	-0.417	0.003 ^a
PostMSW	0.523	<0.001 ^a	-0.418	0.003 ^a
PreSPT	0.487	<0.001 ^a	-0.034	0.816
PreMSW	0.431	0.002 ^a	-0.169	0.240
PreDSW	0.434	0.002 ^a	-0.001	0.996

Table 3. Correlation between CI outcomes and MVI or DoD in the CI group. CI, cochlear implantation; DoD, patient-reported duration of hearing deprivation; DSW, disyllabic word test; MSW, monosyllabic word test; MVI, mean voxel intensity in the surviving voxels; Pre, preoperative; Post, postoperative; SIT, speech intelligibility test; SPT, sentence perception test. ^aTwo-tailed $P < 0.05$.

However, given that VBM analysis for DoD instead of CI outcomes showed no surviving voxels, cerebellum Crus I gray matter atrophy does not seem to be directly related to DoD. This may be because the progression rate of hearing loss varies among individuals and is affected by environmental factors²⁸. Nevertheless, DoD showed a significantly negative correlation with all CI outcomes, indicating that cerebellum gray matter volume and DoD independently affect CI outcomes. In addition, cerebellum gray matter volume showed a stronger correlation not only with CI outcomes but also with preoperative speech intelligibility test compared to DoD (Table 3). Therefore, we can suggest that temporal MRI is required before CI not only for evaluating cochlear and nerve deformities but also for assessing cerebellum volume loss, which can impact the outcome.

Contrast to DoD and preoperative speech intelligibility test results, the age of the implant did not show a significant relationship with CI outcomes. Indeed, the relationship between implant age and CI outcome is controversial^{29,30}. Patients whose age of implant is under 60 are possibly not due to ARHL but other etiology, therefore, comparison with younger age patients should be carefully interpreted. Furthermore, as the results of this study (Fig. 1), the significant association between implant age and DoD may bias the comparison between groups categorized by age. In this study, we recruited patients aged over 70 and employed correlation analysis rather than categorizing patients by age. The results showed no correlation between implant age and CI outcome.

Several limitations of the study should be acknowledged. First, we could not evaluate the long-term postoperative change in speech intelligibility test scores. In addition, older adults may take longer to reach plateau than younger adults, so future prospective studies should consider evaluating follow-up at longer time points, such as at least 1 year³¹. Second, in this analysis, only the cerebellar region commonly included in tMRI of individuals in the CI group was configured as the ROI, so the entire cerebellum could not be analyzed. Third, the factors possibly affecting the cerebellar volume were not completely controlled. These include right-handedness, socio-economic status, and educational level. Forth, although ARHL is the most frequent, heterogeneous etiology of the enrolled patients can bias the result. A larger number of enrolled patients is required to analyze homogeneous etiology. Fifth, since the parameters of the MRI acquisition, including voxel size and inversion time, were different between the CI group and the control group, it may have acted as a systematic confounding factor for the results, including voxel-wise intensity. Lastly, in clinical settings, measuring the degree of gray

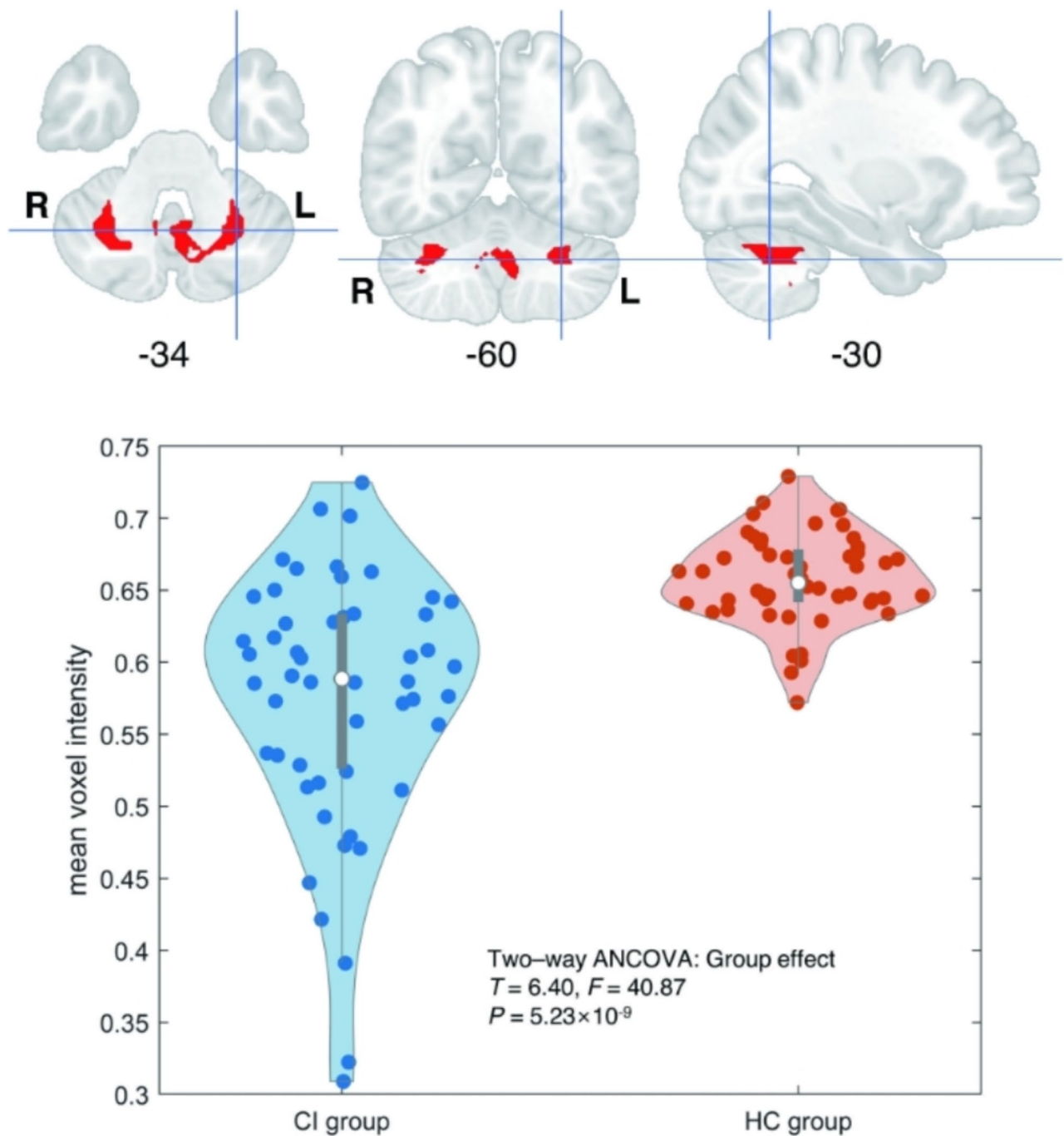


Fig. 3. Binary maps and MVI distributions showing significant intensity differences. Panels show the comparison of CI group with HC group. Voxel-based mapping analyses were performed with one-tailed P_{FWE} threshold of 0.05, adjusted for age, sex, and total intracranial volume. Crosshairs indicate the coordinate with the peak raw Z-value for each comparison. The MNI-152 coordinates in each row under each slice are, from left to right, z (axial), y (coronal), and x (sagittal). The violin plots show the distributions of MVI according to group. The white circle represents the median, the thick gray bar represents the interquartile range, and the thin gray bar represents the distribution range of the values. The width of the violin plot represents the proportion of subjects per group according to the corresponding MVI. ANCOVA, analyses of covariance; CI, cochlear implantation; HC, healthy control; L, left; MNI, Montreal Neurological Institute; MVI, mean voxel intensity of the surviving voxels in the voxel-based morphometry; R, right.

matter atrophy is challenging because it can be significantly affected by sex, age, and skull size unless normalized in the software.

In conclusion, our results suggest that gray matter atrophy of cerebellum Crus I indicates poor outcomes of cochlear implantation in the elderly. It showed a stronger correlation with the outcomes compared to DoD. In addition, the degree of the atrophy and DoD were independent each other in VBM analysis. Clinically, measuring cerebellar atrophy seems to be important for counseling patients considering CI.

Methods

The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study protocol was approved by the institutional review board of Severance Hospital, Seoul, Republic of Korea (4–2022–1081) and was conducted according to the Declaration of Helsinki. Due to the retrospective nature of the study, the need for informed consent was waived.

Study subjects

Among the patients who visited Severance Hospital between January 1, 2010 and January 1, 2022 and underwent CI, the demographic and clinical information of all patients aged ≥ 70 years at the time of surgery was collected using the Clinical Database Repository System of the hospital. Those who met the following inclusion criteria were enrolled in the CI group: (a) diagnosed with post-lingual sensorineural hearing loss with a threshold of 70 dB in both ear by an otolaryngology specialist and underwent successful unilateral CI; (b) underwent preoperative tMRI, PTA, and speech intelligibility test at Severance Hospital within one month; and (c) underwent speech intelligibility test within one month before and 6 and/or 12 months after CI.

The common exclusion criteria applied to the CI group and the healthy control group were as follows: (a) comorbid central nervous system diseases that can affect hearing function or speech perception, such as stroke or traumatic brain injury; (b) evidence of intracranial lesions > 3 mm in diameter on MRI;³² (c) ventriculomegaly with Evans' index > 0.4 ;³³ (d) cerebral white matter hyperintensities with Fazekas scale > 2 ;³⁴ or (e) inadequate image quality/artefact of tMRI.

All patients used hearing aids for at least 1 month before receiving CI and preoperative auditory tests. DoD was collected by asking patients during the consultation for CI, "How long have you been unable to converse with your bare ears?" We enrolled patients aged over 70 years, considering the average age of ARHL onset and its slow progression, to exclude possible late-onset genetic hearing loss^{35,36}.

For detailed analysis, the control group consisted of individuals who underwent a 3D T1 brain MRI at Severance Hospital for health check-up and exhibited no symptoms of hearing loss. They were matched by age and sex with the members of the CI group. The MRI scans of all study subjects were reconfirmed for brain lesions and image quality based on the above exclusion criteria by B.S., the researcher of this study that specializes in neuroimaging analysis.

Audiologic tests

All PTAs were conducted in soundproof booths. First, all patients underwent binaural preoperative PTA by experienced audiologists using a routine method. Air and bone conduction PTA were performed at frequencies of 250, 500, 1000, 2000, 3000, and 4000 Hz, respectively. PTA4 was defined as the mean dB of air conduction pure-tone threshold at frequencies of 500, 1000, 2000, and 3000 Hz, and a higher PTA4 indicated more impaired hearing function³⁷.

The Korean version of the speech intelligibility test was scheduled to be assessed before surgery and postoperatively 12 months after switch-on. The preoperative speech intelligibility test was performed using binaural hearing aids in the sound field, and the postoperative speech intelligibility test was performed in unilateral CI only condition. The dependent variables for this study consisted of the preoperative scores (Pre) and postoperative scores (Post) obtained at around 12 months post-cochlear implantation on three auditory-only listening tests: monosyllabic word test (MSW), disyllabic word test (DSW), and sentence perception test (SPT). This selection was made as the recovery of speech perception typically stabilizes after 6 months from the CI switch-on³⁸. These scores were expressed as percentages. All three tests have been confirmed to exhibit both intra- and inter-rater reliability³⁹. The tests were conducted using samples of words or sentences employing the modified Seoul National University Hospital Speech Perception Test within a noiseless room environment at a stimulation level of 65 dB SPL. The sample words or phrases were pronounced by a single audiologist positioned 1 m away⁴⁰.

Acquisition of MRI

All MRIs were obtained using a 3-Tesla MR Scanner (Achieva, Philips Medical System, Best, The Netherlands) equipped with an 8-channel head coil. The tMRIs were acquired using a 3D fluid-attenuated inversion recovery-volume isotropic turbo spin echo acquisition (3D FLAIR-VISTA) sequence with the following parameters: matrix size of $512 \times 512 \times 64$, voxel size of $0.590 \times 0.590 \times 0.590$ mm, repetition time of 8000 ms, echo time of 273.5 ms, inversion time of 2400 ms, and flip angle of 90° . As the focus of tMRI was on the internal auditory canal, the acquired images typically encompassed regions, such as the anteroventral tip of the temporal pole, internal auditory canal, and a segment of the dorsal area of the cerebellar posterior lobe and flocculonodular lobe. All subjects who underwent tMRI in the CI group also underwent whole-brain 2D FLAIR sequence and tMRI. These additional sequences were utilized to verify whether the subjects exhibited any exclusion criteria and to calculate the total intracranial volume. The 2D FLAIR sequence images were acquired with the following parameters: matrix size of $512 \times 512 \times 22$, voxel size of $0.449 \times 0.449 \times 5.000$ mm, repetition time of 11,000 ms, echo time of 125 ms, inversion time of 2800 ms, and flip angle of 90° . For the brain MRI in the control group, high-resolution axial T1-weighted MRI data were acquired using a 3D fast-field echo magnetization-prepared

rapid gradient-echo sequence. The imaging parameters were as follows: matrix size of $1024 \times 1024 \times 160$, voxel size of $0.234 \times 0.234 \times 1.2$ mm, repetition time of 9.2 ms, echo time of 5.1 ms, and flip angle of 8° .

VBM

VBM is a technique used in neuroimaging to analyze the differences in brain anatomy and structure between different groups of individuals. VBM allows researchers to quantitatively compare the volume and concentration of gray matter, white matter, and cerebrospinal fluid across different brain regions⁴¹.

VBM preprocessing was conducted using SPM 12 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (MATLAB and Statistics Toolbox Release 2020b, The MathWorks, Inc., Natick, Massachusetts, USA). Images that met all inclusion criteria were segmented into GM, WM, and cerebrospinal fluid using the tissue probability maps of SPM 12. Following affine regularization of gray matter and white matter with the East Asian ICBM template, alignment was performed using Diffeomorphic Anatomical Registration through exponentiated Lie Algebra (DARTEL) registration⁴², and normalization to the Montreal Neurological Institute (MNI) space was carried out (matrix size = $79 \times 95 \times 79$, voxel size = $2 \times 2 \times 2$ mm). Subsequently, the images were modulated to preserve the total amount of regional GM and smoothed using a full-width at half-maximum isotropic Gaussian kernel of 8 mm^{43,44}. To minimize edge effects around the border between gray matter and white matter, only voxels with a value ≥ 0.1 within the SUIT, a Spatially Unbiased Atlas Template of the human cerebellum and brainstem, were retained, resulting in a study-specific cerebellar gray matter ROI for voxel-wise statistical analyses. The voxel-wise intensity of each subject was then entered as an independent variable in VBM, masking only the voxels belonging to the ROI.

All voxel-wise statistical analyses were conducted using the TFCE toolbox in conjunction with in-house MATLAB scripts⁴⁵. In all VBM analyses, age at MRI, sex, and total intracranial volume were included as default nuisance regressors⁴⁶. Initially, a general linear model was constructed using the duration of hearing deprivation as the regressor of interest to identify cerebellar gray matter regions exhibiting atrophy with increasing hearing deprivation duration. Subsequently, general linear models were constructed with the duration of hearing deprivation added to the default nuisance regressors to investigate the association between the 12-subitem scores of the SIT assessed in the CI group and the intensity for each voxel within the ROI. To compare the control group with the CI group, two separate general linear models were constructed using a dichotomized group variable (0 for CI and 1 for control), intensity for each voxel within the ROI, and default regressors. The resulting T-values were then Z-transformed and utilized as the basis for permutation-based multiple comparison corrections.

Statistical significance for voxel-wise analyses was set at familywise error-corrected one-tailed $P(P_{FWE}) < 0.05$ using TFCE (26-directions for 3-dimensionality) and 5000 Freedman–Lane non-parametric permutations, a reliable method regardless of the distribution of regressors^{45,47}. All statistical tests were one-tailed given our a priori hypothesis that patients with HL will present with less cerebellar gray matter^{48,49}. Raw statistics without permutations and TFCE were also calculated to define the coordinates of the voxels with the peak Z-values. Statistically significant cerebellar voxels were labeled according to the SUIT atlas and MNI coordinates.

Surviving voxel-based analyses

The voxel-level survival analysis provides a powerful tool for investigating the spatial distribution of brain changes associated with clinical outcomes or disease progression in neuroimaging studies. Surviving voxel-based analysis is a process of re-verification using the average value of voxels at the location that showed statistical significance in the voxel-wise analysis. In this study, it was implemented to simplify the results. To ascertain whether the correlation between DoD and each SIT subitem differs from the correlation between the mean voxel intensity of the surviving voxels in VBM and each SIT subitem score, we aimed to determine which factor, DoD or cerebellar gray matter density in the CI group, exhibits a stronger correlation with each subitem. Consequently, we conducted a Spearman partial correlation analysis, controlling for the default regressors.

Furthermore, two-way analyses of covariance (ANCOVA) with type III sums of squares were conducted to assess the disparity in surviving voxels between the CI group and the control group. Initially, interactions between covariates were examined, and in instances where no significant interactions were observed, a linear regression model was established to assess the goodness-of-fit. Upon demonstrating a statistically significant fit, the difference in surviving voxels between groups was evaluated with adjustments for the default regressors. For all surviving voxel-based analyses, null hypothesis tests utilized one-tailed thresholds, with statistical significance defined as $P < 0.05$.

Statistical analyses

Demographic and clinical data, including the prevalence of risk factors and etiologies for HL, were collected from all study subjects through electronic medical chart review. Statistical analyses of demographic and clinical data were performed using Matlab and R, version 4.2.0 (R foundation, <https://www.r-project.org/>). Demographic and clinical characteristics were compared between groups using a χ^2 test for binary variables, a linear-by-linear association test for ordinal variables with a number less than 2 in at least one cell in the contingency table, an independent t-test for normally distributed continuous variables, or the Mann–Whitney test for non-normally distributed continuous variables. Unadjusted Spearman correlation analyses were implemented to investigate the relationship between the scores of speech intelligibility tests, PTA4 on each side, age, and DoD. All null hypothesis tests of demographic and clinical characteristics were two-tailed, and statistical significance was set at $P < 0.05$.

Data availability

The de-identified data and codes that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

JYK, JYC, KMK, and SHB designed the study. DK and JJ retrieved data. JYK and BS performed the statistical analyses. JYK, BS, JYC, and SHB wrote the manuscript. All authors reviewed and edited the draft manuscript and approved the submission of this manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Severance Hospital, Seoul, Republic of Korea (4–2022–1081) and was conducted according to the Declaration of Helsinki. Due to the retrospective nature of the study, the need for informed consent was waived by the institutional review board of Severance Hospital.

Additional information

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Correspondence and requests for materials should be addressed to S.H.B.

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