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Research article

Reduced grey- and white matter volumes due to unilateral hearing loss following treatment for vestibular schwannoma

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ABSTRACT

Objective: Previous studies of the consequences of unilateral hearing loss (UHL) on the functional-structural organization of the brain has included subjects with various degrees of UHL. We suggest that the consequences of a total loss of hearing in one ear might differ from those seen in subjects with residual hearing in the affected ear. Thus, the main aim of the present study was to compare the structural properties of auditory and non-auditory brain regions in persons with complete UHL to those of normal hearing controls. We hypothesize that the consequences of complete UHL following treatment for vestibular schwannoma will differ between ipsi- and contralateral structures, as well as between right- and left side deafness.
Design: A 3T Siemens Prisma MR-scanner was used. Anatomical images were acquired using a high-resolution T1-weighted sequence. Grey- and white matter volumes were assessed using voxel-based morphometry.
Study sample: Twenty-two patients with left- or right-side unilateral hearing loss. Fifty normal hearing controls.
Results: Reductions in grey- and white matter volumes were seen in cortical and sub-cortical regions, mainly in the right hemisphere including the auditory cortex, lingual gyrus, cuneus, middle temporal gyrus, occipital fusiform gyrus, middle cingulate gyrus and the superior temporal gyrus. Patients displayed reduced grey- and white matter volumes in cerebellar exterior structures ipsilateral to the tumor side.
Conclusion: When compared to controls, right side hearing loss yields more widespread reduction of grey matter volume than left side hearing loss. The findings of reduced grey- and white matter volumes in auditory and non-auditory brain regions could be related to problems with speech perception in adverse listening conditions, increased listening effort and reduced quality of life reported by persons with unilateral hearing loss despite normal hearing in the unaffected ear.

1. Introduction

Recent neuroimaging studies demonstrate that both the right and left hemispheres are responsive to speech sounds, and that not only the auditory cortex, but areas such as the bilateral superior- and temporal gyri as well as left prefrontal- and motor cortices and even the cerebellum are involved in the processing of auditory information, including speech [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Thus, adequate perception and processing of speech and non-speech auditory stimuli and separation of speech stimuli against background noise is hypothesized to rely on a bihemispherically distributed network of brain regions and their interconnections (see e.g. Price [10] and Specht [7] for reviews). Hence, multiple brain regions may be affected by partial or total loss of peripheral hearing, and lesions in single brain regions or disrupted between-region communication may affect auditory functioning [11].

So far, knowledge on the structural consequences of unilateral hearing loss (UHL) on these structures and networks is limited [12, 13]. Unlike those with bilateral hearing loss, persons with UHL are still able to capture auditory stimuli at normal hearing levels using their unaffected ear. However, persons with UHL report considerable difficulties with

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sound source localization, speech perception in noise as well as an increase in listening effort [14, 15, 16]. These difficulties may be hypothesised to be affected not only by lost binaural capabilities, but by the plastic changes in the central nervous system triggered by peripheral asymmetry as well [17].

One cause of UHL in adults is vestibular schwannoma (VS). This is a benign tumor arising from the Schwann cell sheet of the vestibular nerve. In most cases it has a slow growth rate, and the tumor size often remains unchanged over many years [18]. The diagnosis is usually made in adults and presents with UHL, tinnitus and vertigo with or without imbalance [19]. Thus, VS may have major influences on the quality of life, with UHL as one of the consequences [20, 21, 22]. Different treatment options have been put forward and besides observation, surgery will be the typical treatment [23], separated into classical microsurgical interventions or radiotherapy, using gamma knife radiosurgery [24]. The choice of treatment depends on tumor size and patient symptoms, where microsurgery is considered the accepted treatment for larger tumors. Due to resection of the VIII cranial nerve this procedure may cause complete UHL. This may also occur following gamma knife radiosurgery or even in untreated tumors [22, 25, 26].

Functional reorganization of the neuronal network for auditory perception after UHL has been investigated using a range of different techniques (see e.g. Heggdal et al [13] and Eggermont [12] for reviews). Structural alterations on the other hand, are so far less studied and most of the studies at hand have focused on persons with complete bilateral deafness. In that population, both preserved and decreased grey matter (GM) volumes have been reported for the auditory cortices [27, 28, 29, 30]. In older adults with HL, HL severity has been found to correlate to GM volumes. In these populations, functional and structural changes in areas proposed related to higher-order cognitive processes have been observed as well [31]. In persons with bilateral profound hearing loss, Hribar et al [31] found increased GM volumes in the cerebellum as well as the Heschl's gyrus (HG) when compared to normal hearing controls. Their findings are in contrast to some other studies reporting decreased volumes in deaf subjects left cerebellum [27]. It is suggested that these discrepancies might be related to the use of sign language in some subjects, possibly motivating a greater involvement of the cerebellum [31, 32]. In persons with tinnitus and normal hearing, abnormal connectivity patterns have been shown between the primary auditory cortex and the cerebellum [33] and between the cerebellum and the left superior frontal gyrus [34]. Recently, reports of cerebellar involvement beyond the well-known coordination of motor functions are coming forward [8], as it seems to be involved in language processing, cognitive abilities, visuospatial perception, emotion, behaviour and personality as well [9]. Thus, it seems that hearing loss might affect regions involved in higher-order cognitive function due to functional-structural reorganization driven by deteriorated auditory input affecting higher-order perception and processing.

GM and white matter (WM) volume alterations in those with UHL have been investigated recently using voxel-based morphometry. In patients with UHL due to untreated unilateral VS, Wang et al [35] uncovered decreased GM volumes both in primary sensory regions, that correlated to subjective hearing ability, and in cortical areas involved in higher-order cognitive processing, that correlated to HL duration. Comparing subjects with right/left side HL, they found that the lateralization of structural changes was related to the side of the HL, with the two groups mirroring each other. In agreement to some previous studies on functional reorganization following UHL [1, 36, 37] this may suggest that the laterality of the HL will affect ipsi- and contralateral structures differently.

Previous studies of the consequences of UHL on the functional-structural organization of the brain has included subjects with various degrees of UHL. We suggest that the consequences of a total loss of hearing in one ear might differ from those seen in subjects with residual hearing in the affected ear. Thus, the main aim of the present study was to compare the structural properties of auditory and non-auditory brain regions in persons with complete UHL to those of normal hearing controls. We hypothesize that the consequences of complete UHL following treatment for VS will differ between ipsi- and contralateral structures, as well as between right- and left side deafness.

2. Design and study sample

2.1. Subjects

Three groups of subjects were recruited. These were normal hearing controls, persons with right side UHL and persons with left side UHL.

Patients with UHL following treatment of vestibular schwannoma were recruited to be part of the study and recruited and tested while in the clinic for ordinary follow-up appointments. Inclusion criteria were complete deafness (pure tone thresholds 0.25–8 kHz >120 dB HL) in one ear following treatment of vestibular schwannoma, and normal hearing (pure tone average for frequencies 0.5, 1, 2 & 4 kHz [PTA] ≤ 25 dB HL) in the contralateral ear. Exclusion criteria were metal or ferromagnetic implants or braces, other known serious neurological or psychiatric illnesses and pregnancy.

In total, twenty-two patients (9 males) were included, aged 25–62 years ($M = 48$, $SD = 10.7$). HL duration ranged from two to 16 years ($M = 6$, $SD = 4.3$) and was defined as years from complete loss of hearing in one ear, as confirmed by pure tone audiometry in patient records. Twelve patients had received microsurgical treatment of the tumor; four patients had been treated with gamma knife therapy, while the remaining six patients had received both treatments sequentially.

Twelve patients (5 males) had right side HL. These were aged 25–62 years ($M = 48.9$, $SD = 9.9$) and HL duration ranged from 2 to 16 years ($M = 7.6$, $SD = 5$). Five of the patients with right side HL had received microsurgical treatment only, while one patient had received gamma knife therapy only. The remaining six had received both treatments sequentially.

Ten patients (4 males) had left side HL. These were aged 27–59 years ($M = 46.5$, $SD = 11.9$) and HL duration ranged from 2 – 10 years ($M = 4.2$, $SD = 2.4$). Seven of the patients with left side HL had received microsurgical treatment while the remaining three had received gamma knife therapy.

Normal hearing persons were recruited to a control group. Inclusion criteria were normal hearing in both ears (≤25 dB HL at frequencies 0.25–8 kHz). Exclusion criteria were metal of ferromagnetic implants or braces, known neurological or psychiatric illness and pregnancy. Fifty persons (25 males) were included in the control group, aged 23–58 years ($M = 36$, $SD = 10$).

All subjects were right-handed. Handedness was determined according to the Edinburgh Inventory using an exclusion criterion set to 13 of 15 possible points [38]. All subjects signed a letter of consent prior to testing. The Norwegian Regional Committees for Medical and Health Research Ethics provided advance approval for the project (Project reference: 2013/1282-3).

2.2. MR scanning & analysis

MR scanning was performed using a 3T Siemens Prisma scanner and a 20-channel head/neck coil. Scans of patients and controls were booked alternately to reduce the effect of eventual changes in the scanner over time. Anatomical images were acquired using a high-resolution T1-weighted (MPRAGE) MR sequence with the parameters: 192 sagittal slices, 1 mm isotropic voxel, echo time (TE) = 2.28 ms, repetition time (TR) = 1800ms, inversion time (TI) = 900ms, field of view (FOV) = 256 × 256mm and flip angle (FA) = 8.

The structural images were processed using Statistical Parametric Mapping software (SPM12) in MATLAB ver. R2018b. First, images were segmented into grey and white matter, normalized into the MNI reference space, and smoothed with a 6 mm Gaussian kernel. The statistical analysis of the data was performed as general linear models, as implemented in SPM. As data served the modulated [39, 40], normalized grey and white matter images. To detect differences between the three groups of subjects, a one-way ANOVA was carried out. Then, post-hoc independent samples t-tests were used to determine differences between each of the groups (controls, right UHL and left UHL). Also, to assess whether any grey- or white matter alterations in the patient groups as compared to normal hearing controls overlapped, a global conjunction analysis including the two patient groups was carried out. All data reported were corrected for multiple comparisons using a voxel-level threshold of $p < 0.05$ family-wise-error corrected (FWE) and a cluster size ≥10.

3. Results

VBM analyses revealed reduced cerebellar GM and WM volumes in both cortical and sub-cortical regions in patients when compared to controls (controls > patients) (see Tables 1 and 2). No areas showed increased GM or WM volumes in patients as compared to normal hearing controls. A global conjunction analysis showed that the GM volume reduction in patients with right and left UHL as compared to normal hearing controls overlapped in an area corresponding to the right middle temporal gyrus (BA 21) ($T = 5.29$ [MNI 66, -64, 4], 10 voxel). No differences were found in WM volumes between patient groups. Figure 1 shows areas with reduced grey- and white matter volumes in persons with unilateral hearing loss as compared to normal hearing controls.

4. Discussion

Compared to controls, patients with UHL after treatment for VS displayed reduced GM and WM volumes in cerebellar exterior structures ipsilateral to the tumor side. This is in line with previous studies in this population, where such changes have been observed both pre- [35] and post [41] surgical treatment of VS. Altered GM volumes have also been reported in the cerebellum of patients with bilateral HL without VS or any surgical intervention [27, 28]. Thus, the GM and WM reductions observed in our subjects could be the combined result of reduced vestibular ipsilateral projections to cerebellar structures pre- and post-treatment, and a consequence of the surgical intervention in the area. The contribution of surgery and pretreatment conditions to the final, long-term structural properties of the cerebellum cannot be quantified in our patients, as they had received varying treatments for their tumors and no measures of GM/WM were made prior to treatment. Nevertheless, considering recent reports of cerebellar involvement in higher-order language processing [8, 9], reduced cerebellar GM may play a role in the difficulties that persons with UHL experience e.g. in adverse listening scenarios, despite preserved normal hearing sensitivity in the unaffected ear [17]. Further investigations are however needed to better understand this relationship. Future studies should also aim to include measures of vertigo and imbalance, to investigate eventual correlations between the structural properties of the cerebellum and such measures. This would be relevant given the well-known involvement of the cerebellum in motor functions, and the fact that persons with VS often experience vertigo and/or imbalance both pre- and post-treatment.

More importantly, reduced GM volumes were also seen in regions beyond those potentially affected by the surgical intervention, and some differences between right- and left side UHL were found. Compared to controls, those with right side UHL show loss of GM in more areas than those with left side UHL. Areas that were affected in patients with right side UHL included both sides lingual gyrus and right-side middle temporal gyrus, cuneus, middle cingulate gyrus as well as left side occipital fusiform gyrus. The lingual gyrus and the cuneus belong to the striate cortex and take part in processing of visual stimuli. These regions have also been reported to be involved in early stage multimodal sensory integration [42, 43], and persons with hearing loss have previously been found to have decreased functional connectivity in these regions [44].

Table 1. Grey matter volume differences between normal hearing controls and patients with right or left side single-sided deafness (SSD). The primary maximum per cluster is set in bold.

GREY MATTER VOLUME DIFFERENCES						
Control > Right UHL						
Statistical values			**MNI-Coordinates**			**Anatomical location**
Cluster level		Peak-level	*x*	*y*	*z*	Structure (Brodmann area)
#voxel	pFWEcorr	*T*				
2346	**< 0.001**	**9.70**	**39**	**-66**	**-52**	**Right Cerebellum exterior**
		9.40	46	-63	-28	
		8.96	39	-57	-54	
109	**< 0.001**	**7.34**	**0**	**-68**	**0**	**Left and right Lingual Gyrus**
		5.69	-3	-78	-12	Left Lingual Gyrus
24	**0.005**	**6.65**	**69**	**-36**	**-4**	**Right middle temporal gyrus (BA21)**
74	**< 0.001**	**6.61**	**9**	**-87**	**12**	**Right Cuneus (BA17)**
95	**< 0.001**	**5.85**	**8**	**-70**	**-14**	**Right Cerebellum exterior**
12	**0.012**	**5.68**	**38**	**-40**	**-34**	
17	**0.008**	**5.65**	**-40**	**-80**	**-20**	**Left occipital fusiform gyrus (BA19)**
11	**0.013**	**5.55**	**4**	**-26**	**45**	**Right middle cingulate gyrus (BA31)**
23	**0.006**	**5.42**	**68**	**-45**	**2**	**Right middle temporal gyrus (BA21)**
Control > Left UHL						
Statistical values			**MNI-Coordinates**			**Anatomical location**
Cluster level		Peak-level	*x*	*y*	*z*	**Structure (Brodmann area)**
#voxel	pFWEcorr	*T*				
10	**0.014**	**6**	**64**	**-16**	**10**	**Superior temporal gyrus (BA41)**
35	**0.003**	**5.81**	**-40**	**-72**	**-46**	**Left cerebellum exterior**
		5.45	-44	-64	-46	
23	**0.006**	**5.66**	-46	-66	-30	**Left cerebellum exterior**
		5.55	-40	-76	-32	

Table 2. White matter volume differences between normal hearing controls and patients with right or left side single-sided deafness (SSD). The primary maximum per cluster is set in bold.

WHITE MATTER VOLUME DIFFERENCES						
Control > Left UHL						
Statistical values			**MNI-Coordinates**			**Anatomical location**
Cluster level		Peak-level	*x*	*y*	*z*	Structure (Brodmann area)
#voxel	pFWEcorr	*T*				
70	**< 0.001**	**6.16**	**-15**	**-34**	**-40**	**Left cerebellum exterior**
Control > Right UHL						
Statistical values			**MNI-Coordinates**			**Anatomical location**
Cluster level		Peak-level	*x*	*y*	*z*	Structure (Brodmann area)
#voxel	pFWEcorr	*T*				
111	**< 0.001**	**6.29**	**10**	**-18**	**-33**	**Right brainstem**
17	**< 0.001**	**5.23**	**-3**	**-15**	**-18**	**Left ventral diencephalon**

Combined with the findings of reduced GM in the contralateral occipital fusiform gyrus (corresponding to Brodmann area 19), another higher-order visual region, it seems that right side UHL alters GM volumes in several regions involved in the early-stage integration of auditory and visual stimuli. Thus, right side UHL seems to affect the structural properties of several cortical structures in non-auditory areas, while such structures are not affected in those with left side UHL.

In those with right side UHL, reduced GM was also seen in ipsilateral middle temporal gyrus and the middle cingulate gyrus, in regions corresponding to Brodmann areas 21 and 31. The middle temporal gyrus is involved in several cognitive processes including processing of language [45].

The reduction of WM volume in the left portion of the diencephalon in those with right side UHL could be related to structural alterations of the thalamus, which is a major component of the diencephalon [46]. The main projections leaving the thalamus comprise projections to all areas of the cortex. The medial geniculate body represents the main auditory-responsive portion of the thalamus and this structure is seen as an information bottleneck for the neural representations of auditory stimuli to the auditory cortex [47]. Those with left side UHL only show reduced GM in an area corresponding to the right-side auditory cortex (BA41), when compared to controls. As proposed by Amaral et al [46] such sub-cortical structural alterations are likely to occur alongside cortical reorganization, such as that seen in the right auditory cortex in

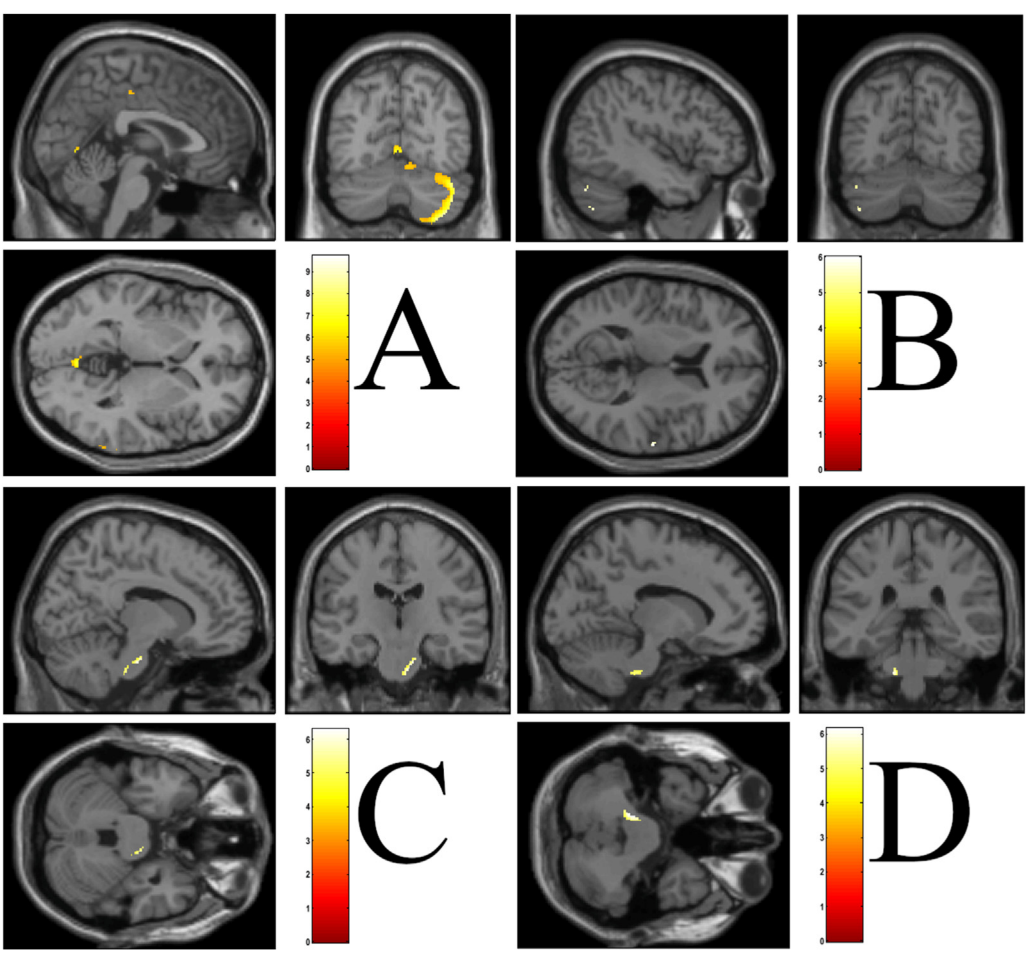

Figure 1. Areas with reduced grey- and white matter volumes in persons with unilateral hearing loss as compared to normal hearing controls. A: Grey matter reductions in persons with right side deafness. B: Grey matter reductions in persons with left side deafness. C: White matter reductions in persons with right side deafness. D: White matter reductions in persons with left side deafness. All data reported are corrected for multiple comparisons using a voxel-level threshold of $p < 0.05$ family-wise-error corrected (FWE). Clusters are superimposed on the MNI template implemented in SPM12.

our patients. We suggest that there is a bilateral relationship between the structural changes in cortical and sub-cortical structures, reflecting that the communication between such regions is altered following loss of peripheral input.

Both left- and right side UHL seems to affect GM volumes in right-side temporal lobe structures. The reduction of GM volume overlapped between the two patient groups in an area corresponding to the right middle temporal gyrus. No affection of left side temporal GM is revealed in our results. More regions show reduced GM volumes in those with right UHL than those with left UHL when compared to normal hearing controls. Considering the suggested key role of the right hemisphere in speech comprehension in adverse listening conditions [48, 49], we suggest that these reduced GM volumes might be related to the difficulties persons with UHL experience when trying to perceive speech in noisy environments. The retained structural properties of the temporal structures in the left hemisphere could then be hypothesized to be responsible for the near normal perception of speech without the presence of noise in persons with UHL. This would be in line with Chang et al [17], who suggested that the problems faced by persons with UHL could be the result of not only the loss of binaural input, but of the functional-structural consequences of such deprivation as well.

5. Conclusion

Patients with unilateral hearing loss after treatment for vestibular schwannoma have reduced GM and WM volumes in the cerebellum and in several cortical and sub-cortical areas when compared to healthy controls. Altered structural properties in the cerebellum are proposed caused by long-term unilateral vestibular input as well as surgical intervention. A limitation to the present study is the unknown effect of the various treatment methods the patients had received, and the subsequent effect of these on GM and WM volumes. The findings of reduced GM volumes in non-auditory brain regions could possibly be related to problems with speech perception in adverse listening conditions, increased listening effort and reduced quality of life reported by persons with UHL despite normal hearing in the unaffected ear [14, 15, 16]. GM volume loss in right side temporal structures might be related to difficulties with perceiving speech in noise. Right side UHL possibly motivates more widespread structural alterations than what seen in left side UHL.

Declarations

Author contribution statement

Peder O. Laugen Heggdal, Karsten Specht: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kristina S. Larsen, Jonas Brännström, Hans Jørgen Aarstad: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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