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DIFFUSION TENSOR IMAGING AND MR MORPHOMETRY OF THE CENTRAL AUDITORY PATHWAY AND AUDITORY CORTEX IN AGING

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Abstract—Age-related hearing loss (presbycusis) is caused mainly by the hypofunction of the inner ear, but recent findings point also toward a central component of presbycusis. We used MR morphometry and diffusion tensor imaging (DTI) with a 3 T MR system with the aim to study the state of the central auditory system in a group of elderly subjects (>65 years) with mild presbycusis, in a group of elderly subjects with expressed presbycusis and in young controls. Cortical reconstruction, volumetric segmentation and auditory pathway tractography were performed. Three parameters were evaluated by morphometry: the volume of the gray matter, the surface area of the gyrus and the thickness of the cortex. In all experimental groups the surface area and gray matter volume were larger on the left side in Heschl's gyrus and planum temporale and slightly larger in the gyrus frontalis superior, whereas they were larger on the right side in the primary visual cortex. Almost all of the measured parameters were significantly smaller in the elderly subjects in Heschl's gyrus, planum temporale and gyrus frontalis superior. Aging did not change the side asymmetry (laterality) of the gyri. In the central part of the auditory pathway above the inferior colliculus, a trend toward an effect of aging was present in the axial vector of the diffusion (L1) variable of DTI, with increased values observed in elderly subjects. A trend toward a decrease of L1 on the left side, which was more pronounced in the elderly groups, was observed. The effect of hearing loss was present in subjects with expressed presbycusis as a trend toward an increase of the radial vectors (L2L3) in the white matter under Heschl's gyrus. These results suggest that in addition to peripheral changes, changes in the central part of the auditory system in elderly subjects are also present; however, the extent of hearing loss does not play a significant role in the central changes.

Key words: presbycusis, aging, auditory cortex, auditory pathway, MR morphometry, diffusion tensor imaging.

INTRODUCTION

Hearing loss accompanying aging, called presbycusis, is one of the prominent sensory deficits in the elderly. Presbycusis is regularly diagnosed by audiometric methods, which in general comprise pure tone and speech audiometry. Since a major component of presbycusis is the loss of hair cells (Schuknecht and Gacek, 1993), the results of pure tone audiometry mostly reflect the deteriorated function of the auditory periphery, whereas speech audiometry also informs about the changes in the function of the central parts of the auditory system. Recent results of animal experiments point toward an important central component of presbycusis, which is evident mainly from the pathological processing of the temporal parameters of a sound (Eggermont, 1993; Walton et al., 1998; Mendelson and Ricketts, 2001; Caspary et al., 2008; Recanzone et al., 2011; Suta et al., 2011) and on the cellular level, on the dysfunction of a specific population of interneurons containing calcium binding proteins, particularly parvalbumin (Ling et al., 2005; Ouda et al., 2008, 2012). Both of these facts, accompanied by decreases of inhibitory neurotransmitters (Caspary et al., 1990; Burianova et al., 2009; Syka, 2010), point toward altered inhibition in the auditory cortex during aging. The results of many audiological studies (Mazelová et al., 2003; Hwang et al., 2007; Gates et al., 2008; Anderson et al., 2011; Humes et al., 2012) support the existence of a central component of presbycusis, yet direct proof is still missing.

Recent developments in magnetic resonance imaging (MRI), which enable the detection of changes in brain structure and function on a detailed level, promise to give insight into the mechanisms underlying the central

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Abbreviations: AC, auditory cortex; AP, auditory pathway above IC; DTI, diffusion tensor imaging; EP, elderly subjects with expressed presbycusis; FA, fractional anisotropy; GFS, gyrus frontalis superior; GM, gray matter; HG, Heschl's gyrus; IC, inferior colliculus; MD, mean diffusivity; MP, elderly subjects with mild presbycusis; PT, planum temporale; ROI, region of interest; SNHL, sensorineural hearing loss; V1, visual cortex; WM, white matter; WM_HG, white matter under Heschl's gyrus; YC, young subjects with physiologic hearing/young controls.

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component of presbycusis. MRI experiments are focused either on changes in the functional activity of the cortex examined by functional MRI (fMRI) or on morphological changes in the gray and white matter. MRI morphometry provides high resolution structural images focused on measuring the thickness, the overall volume as well as the surface area of the gray matter. One of the most commonly used techniques is voxel based morphometry (VBM) the main advantage of which is the possibility to compare anatomical differences throughout the whole brain with minimal subjective manual evaluation (Ashburner and Friston, 2000).

Similar methods might also be used for evaluating the state of the white matter, but diffusion tensor imaging (DTI) is generally considered as the most suitable examination technique. DTI uses water solubility, especially its isotropic diffusion properties, to evaluate microscopic tissue changes (Beaulieu, 2002). These changes are expressed by fractional anisotropy (FA; normalized value representing the degree of anisotropy of diffusion), mean diffusivity (MD; average rate of diffusion independent of direction) and axial (L1) and radial (L2L3) diffusivity (average rate of diffusion independent of direction represented by eigenvalues of the diffusion tensor) (Basser and Jones, 2002).

MR morphometry and DTI are ideal for detecting structural changes in the human brain. They have been previously used especially in research into several disorders of the central nervous system, such as cognitive decline, Alzheimer's disease, epilepsy, multiple sclerosis, schizophrenia and also hearing loss (Stebbins and Murphy, 2009; Madden et al., 2012). Several recent publications have described morphometric changes in the auditory cortex and in other parts of the cortex accompanying hearing loss. Decreases in the gray matter volume of the superior temporal gyrus (STG) and superior and medial frontal gyri were found in subjects with hearing loss; however, they were not present in subjects with hearing loss and tinnitus (Husain et al., 2011). In contrast to this, (Boyen et al., 2013) reported increases in gray matter volume in the superior and middle temporal gyri both in hearing impaired subjects and also in hearing impaired subjects with tinnitus in comparison with controls. Decreases were found in their study in both impaired groups in the superior frontal gyrus and occipital lobe. Congenital deafness affected predominantly the white matter and caused a decrease in its volume in the left posterior STG without any significant effect on the gray matter in this area (Shibata, 2007). Gray matter asymmetries in deaf persons were found to be similar overall to those in hearing persons with a larger planum temporale and HG in the left hemisphere (Emmorey et al., 2003; Penhune et al., 2003; Shibata, 2007). Previous DTI analysis of the auditory tract and AC showed changes in the auditory pathway associated with sensorineural hearing loss (SNHL) (Chang et al., 2004; Lin et al., 2008).

The aim of this study was to evaluate age-related as well as hearing-related changes in the acoustic pathway and auditory cortex and in related areas by measuring the DTI parameters of the white matter and changes in MR morphometric parameters such as the thickness, overall volume and surface area of the gray matter. The experiments were performed in two groups of aged subjects (one with mild presbycusis and one with expressed presbycusis) and in a control group of young subjects.

EXPERIMENTAL PROCEDURES

Subjects

Fifty-four volunteers were examined in this study: 20 young subjects with physiological hearing (YC) (n = 20 for morphometry, mean age ± SEM 24.34 ± 0.51, 11 men and nine women; n = 12 for DTI; 25.3 ± 0.72; four men and eight women), 17 elderly subjects with mild presbycusis (MP) (n = 17 for morphometry, mean age ± SEM 67.9 ± 0.45; five men and 12 women; n = 12 for DTI, 68.04 ± 0.6; five men and seven women) and 17 elderly subjects with expressed presbycusis (EP) (n = 17 for morphometry, mean age ± SEM 70.38 ± 1.18; five men and 12 women; n = 15 for DTI, 70.43 ± 1.34; nine men and six women). There was no significant difference in age between the two elderly groups (unpaired t-test, GraphPad Prism). All subjects were right handed according to the adapted Edinburgh handedness inventory. All subjects denied any previous otologic surgery, vestibular lesion, tinnitus, severe head trauma, lesion of the facial nerve, disorder of the cervical spine, self-reported central nervous system disorder or any contraindication for safe MRI scanning. None of the subjects was a musical professional, but several in both elderly groups played musical instruments regularly during their youth. Otoscopic examination with removal of cerumen and confirmation of an intact tympanic membrane were performed in all examined subjects. The examination procedures were approved by the Ethics Committee of the University Hospital Motol, Prague.

Assesment of auditory function

For assessing the hearing abilities of all subjects, the following procedures were used: tympanometry, pure tone audiometry in an extended frequency range and speech audiometry. Audiometric investigations were performed in a sound attenuated chamber; all measurements were performed monaurally, and the ears of each subject were tested successively.

Tympanometry was performed with an Interacoustics AZ26 tympanometer to confirm optimal middle ear conditions and an intact tympanic membrane. For pure tone audiometry over an extended frequency range from 125 Hz to 16 kHz, a Madsen Orbiter 922, Version 2, audiometer was used, calibrated by the Czech Institute of Metrology according to the Czech State Norm and the European Standards EN ISO 389-1and EN ISO 389-5. Acoustical signals were delivered monaurally via Sennheiser HAD 200 high-frequency headphones. Audiograms were measured in one-octave steps at frequencies ranging from 125 Hz to 8 kHz and then at

10, 12.5 and 16 kHz. Hearing thresholds were detected with a resolution of 5-dB steps; the contralateral ear was masked if necessary. Bone conduction testing was performed to exclude possible elevated thresholds due to conductive hearing loss. Speech audiometry was examined with an Interacoustics AC40 clinical audiometer and Sennheiser HDA 200 headphones using a standard CD recording of Czech word audiometry according to Seeman (1960). The results of hearing evaluation were used to determine the state of presbycusis.

MRI measurements

All MR measurements were performed using a Siemens Trio 3T MR system and a 12-channel head coil. For diffusion tensor imaging (DTI) a spin-echo EPI sequence was used with the parameters repetition time (TR), echo time (TE) TR/TE = 8000/88 ms (some subjects were measured with TR/TE = 9100/96 ms), iPAT = 2, 64 diffusion directions, $b = 0/1100$, voxel size $2 \times 2 \times 2$ mm. A 3D structural image was acquired by using the magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the parameters (TI – inversion time) TI/TR/TE = 900/2300/4.63 ms. The structural image was used for morphometric analysis and for automatic generation of a mask of the white matter under Heschl's gyrus (WM_HG). A B_0 field map for the correction of geometric distortions of diffusion-weighted EPI data was acquired by product B_0 field mapping double gradient echo sequence.

MRI post-processing: morphometry. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite (Fischl, 2012), which involves several processing steps described in the following papers: Dale and Sereno (1993), Sled et al. (1998), Dale et al. (1999) and Fischl and Dale (2000), Fischl et al. (2001), Segonne et al. (2004), Segonne et al. (2007). Then, automatic parcellation of the cerebral cortex into units based on gyral and sulcal structure was performed (Desikan et al., 2006) using the Destrieux probabilistic atlas (Destrieux et al., 2010) for parcellation of the anterior transverse temporal gyrus – Heschl's gyrus (HG), planum temporale (PT) and inferior frontal gyrus (Fig. 2) and the atlas provided by the Martinos Center for Biomedical Imaging and the Institute of Neurosciences and Biophysics (https://surfer.nmr.mgh.harvard.edu/fswiki/BrodmannAreaMaps) for parcellation of the primary visual area V1 (Brodmann area 17). Finally, morphometric parameters, such as gray matter volume, the gyral surface area and the average thickness of the gray matter of the cortical areas of interest were computed.

MRI post-processing: DTI. The post-processing of DTI data, diffusion tensor calculation and tractography were done by means of the FMRIB Software Library (Jenkinson et al., 2012). DTI post-processing involved eddy-current correction, motion correction and

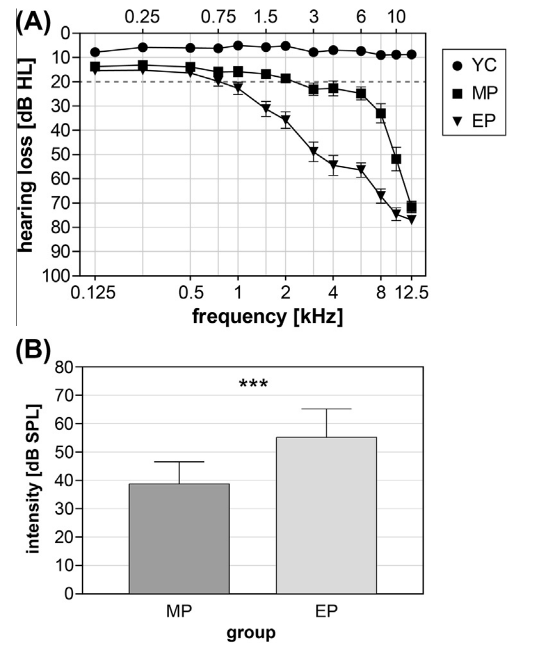

Fig. 1. (A) Hearing thresholds of all three groups (mean ± SEM). All pair-wise comparisons between the three groups (one-way ANOVA; post hoc Tukey test) at frequencies $\geqslant 1$ kHz (frequencies with hearing loss exceeding the physiological range of 20 dB; marked as broken line) show significant differences at $p < 0.001$, apart from the difference between the MP and EP for 1 kHz and 12.5 kHz. (B) Comparison of intensity levels (dB SPL) for 100% speech discrimination score (SDS) in MP and EP (mean ± SEM, $^{***}p < 0.001$, unpaired *t*-test).

correction of geometric distortions of DTI data caused by B_0 inhomogeneity (Jezzard and Balaban, 1995).

White matter probabilistic tractography (Behrens et al., 2007) was done using BEDPOSTX and PROBTRACKX tools and a model of 2 crossing fibers. The seed mask of the WM_HG was automatically generated from the results of the parcellation of the 3D structural dataset, which was defined as a 1-mm-thick volume projected from the spatially reconstructed WM/GM boundary surface toward the white matter side. This volume was transformed to a mask in DTI voxel space with correction for partial volume effects and spatial registration by using Freesurfer tools (Greve and Fischl, 2009).

To perform tractography of the auditory pathway from the inferior colliculus (IC) to HG (Fig. 3), masks of the IC on both sides of the brainstem were generated as spherical ROIs of three voxels in diameter. The position of the IC was manually defined on the $b = 0$ DTI image. To eliminate the risk of estimating spurious tracts (such as tracts crossing the gyrus), a mask of the brain with excluded cortex and ventricles was generated from Freesurfer's parcellation dataset. Furthermore, the termination mask under the IC and an exclusion mask of the central sagittal slice (to exclude interhemispheric tracts) and a coronal mask crossing the rostral thalamus area were automatically defined. Additional exclusion ROIs were manually drawn in several subjects to eliminate spurious tracts.

For tractography of the auditory pathway from the IC to HG, the "multiple masks" mode of PROBTRACKX

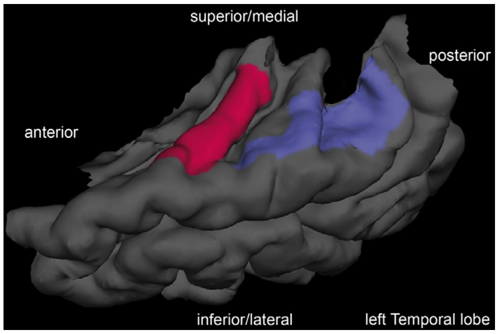

Fig. 2. 3D visualization of the temporal lobe of one subject. The colored areas represent ROIs in the auditory cortex (Heschl's gyrus – red, planum temporale – blue) used for the morphometric measurements. The cortical surface is clipped to allow visibility of the auditory cortex located deeper in the lateral sulcus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was used. The resulting IC–HG tract probabilistic maps were converted to masks by upper thresholding to 10% of the total tractographic streamlines found in a particular pathway tracking.

The masks of IC–HG tracts (denoted as AP) and the masks of WM_HG alone were used for calculating the mean DTI indices: fractional anisotropy (FA), mean diffusivity (MD), first eigenvalue (L1) and mean of the second and third eigenvalues (AvgL2L3) of the diffusion tensor.

Statistical methods

The data were analyzed using a linear mixed model, with the subject group and ROI laterality and their interaction modeled as fixed effects. The inter-individual variability (subject-specific offset within the dependent variable values) was modeled as a random effect. There were five explanatory variables in the model: indicator of age (YC vs. MP), indicator of presbycusis (MP vs. EP), laterality (coded as -1 for left side and 1 for the right side) and two interaction terms (EP vs. laterality; YC vs. laterality). For each measured morphometric or DTI index (dependent variable), a separate model was fitted to explain its dependence on the explanatory (independent) variables. For each dependent variable, we therefore tested five specific hypotheses regarding the effects on the variables of interest:

H1. There is an effect of presbycusis.

H2. There is an effect of age.

H3. There is a laterality difference.

H4. The laterality effect is altered in EP compared to MP.

H5. The laterality effect is different between YC and MP.

The model results were also further explored and interpreted using parameter estimates and boxplots.

Formally, each of the above hypotheses was assessed by statistically testing the corresponding null hypothesis of zero effect/difference. Statistical analyses were performed in environment R (Team RDC, 2010) using the package nlme (Pinheiro et al., 2010).

Two significance thresholds in the analysis were used. Firstly, the uncorrected significance level of $p = 0.05$ for each test controls the probability of false detection of each effect under the validity of the null hypothesis at 5%. However, given the multitude of hypotheses as well as the multitude of related tests for each of the hypotheses (e.g., testing the effect of age on each of four partially related DTI measures), the overall probability of spurious detection of at least one effect using the uncorrected significance threshold in the case of the validity of all null hypotheses (no effects) is far above 5%. In particular, on average two out of the 40 effects tested in the DTI section of analysis and three out of the 60 effects in the VBM section of analysis can be expected to show spurious/false significance under the hypothesis of no true effect at all.

Therefore, the results obtained using a conservative approach to this issue – the application of a Bonferroni correction for multiple testing – were marked separately. While likely over-conservative due to the intricate dependence of the hypotheses in our case, this correction provides a robust control of the family-wise error rate – the probability of having more than zero false detections under the global null hypothesis (no true effects) – under 5%. In other words, in the context of the Bonferonni correction, we control the significance level of the global null hypothesis test at 0.05 (global Type I error probability less than 5%, 'experimentwise alpha') by making the decisions regarding the individual null hypotheses tests based on using a 'corrected' significance level of $0.05/N$ ('testwise alpha'), where N is the number of hypotheses tested.

For transparency, the p-values are provided in full, with test results using both methods separately marked.

RESULTS

State of hearing

The control group of young subjects (YC) displayed normal hearing with thresholds not exceeding 20 dB above the values typical for their age. On the basis of the recorded hearing thresholds and in comparison with the ISO 7029 norm (statistical distribution of hearing thresholds) specified for their age, the elderly patients were divided into two groups. The group called "elderly with mild presbycusis" (MP) showed physiological auditory thresholds ($\leqslant$20 dB) similar to the young control group at frequencies up to 2 kHz. There was a small but steady increase of thresholds at higher frequencies with a 75-dB hearing loss at 12.5 kHz and no hearing at 16 kHz. The group "elderly with expressed presbycusis" (EP) had hearing thresholds elevated into the worse 25% of the population according to the ISO 7029 norm specified for their age and gender (at frequencies 2, 4 and 8 kHz), therefore the EP group's average threshold started to exceed the physiological range at 1 kHz and reached an 80-dB hearing loss at 12.5 kHz with no hearing at 16 kHz. No significant differences between

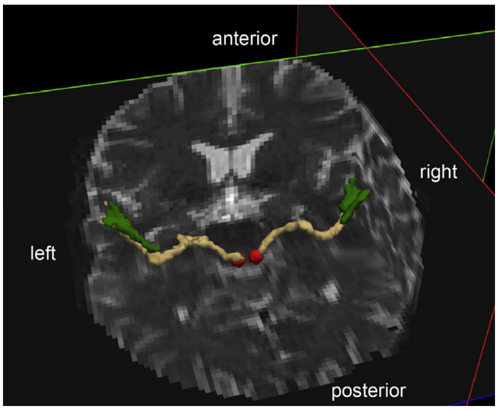

Fig. 3. 3D visualization of three ROIs on both sides in the portion of the auditory pathway (beige) between the IC (red) and the white matter below Heschl's gyrus (green) of one subject. For the DTI white matter analysis, ROIs were overlaid with a diffusion $b = 0$ image (displayed in its original resolution) for each subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1. *p*-Values of the modeled effects for morphometric indices (value 0.000 corresponds to $p < 0.001$). The gray shading highlights all *p*-values lower than 0.05, corresponding to uncorrected testing

Heschl's gyrus	Hearing	Age	Laterality	Hearing vs. laterality	Age vs. laterality
Gray volume [mm^3]	0.7804	*0.0000	*0.0002	0.8024	0.2533
Surface area [mm^2]	0.9372	0.0113	*0.0000	0.6003	0.176
Thickness average [mm]	0.9788	*0.0000	0.7361	0.7358	0.804
Planum temporale					
Gray volume [mm^3]	0.722	*0.0000	*0.0002	0.8833	0.8689
Surface area [mm^2]	0.7207	0.0069	*0.0001	0.9182	0.8565
Thickness average [mm]	0.9455	*0.0000	0.8516	0.9662	0.4103
Visual cortex (V1)					
Gray volume [mm^3]	0.4019	0.0029	*0.0000	0.9903	0.6955
Surface area [mm^2]	0.9376	0.0871	*0.0000	0.1634	0.4273
Thickness average [mm]	0.3389	0.0078	0.0259	0.337	0.6768
Gyrus frontalis superior					
Gray volume [mm^3]	0.7132	*0.0000	0.0466	0.182	0.6461
Surface area [mm^2]	0.5755	*0.0000	0.011	0.2325	0.8975
Thickness average [mm]	0.8081	*0.0000	0.2602	0.502	0.1076

*The asterisk denotes a significant effect under the conservative Bonferroni correction controlling the family-wise error rate among all the morphology effects hypothesis tests at 5% (adjusted threshold padjust = 0.05/60 = ~0.0008)

the left and right ears were found; therefore the thresholds from both ears were merged together. The comparison of thresholds at all frequencies above 1 kHz (exceeding physiologic range) (Fig. 1A) showed significant differences between all three groups (one-way ANOVA, Tukey's multiple comparison test, $p < 0.001$) with the exception of comparing MP vs. EP at 1 ($p = 0.0372$) and 12.5 kHz ($p = 0.0891$). Tympanometric examination showed a type A curve (normal pressure in the middle ear cavity with preserved mobility of the tympanic membrane and ossicular chain) in all subjects. Speech audiometry was performed to confirm the deterioration of hearing in elderly subjects (Fig. 1B). The intensity level at which volunteers reached a 100% speech discrimination score showed a significant difference when MP vs. EP were compared (unpaired *t*-test, $p < 0.0001$) (see Fig. 1B).

Changes in the gray matter investigated by MR morphometry

The results of the gray matter morphometry are summarized in Table 1 and in Fig. 4.

The effect of age was found to be significant or to show a strong trend in all analyzed areas and parameters (apart from the gyral surface area for V1). In all parameters the values for the elderly were lower. Laterality, i.e. differences in the parameters between the left and right hemispheres, was found to be significant for the gray matter volume and gyral surface area in the auditory cortex areas (HG and PT; higher values on the left side) and V1 (higher values on the right side). In the frontal cortex (GFS), a trend toward larger values on the left side was present.

We did not observe any differences in laterality (with the exception of a prevalence of the right side in the V1) in the average thickness of the cortex. Aging did not influence the laterality parameters. No significant difference in any of the parameters was found between the subjects with mild and expressed presbycusis.

Changes of white matter investigated by DTI

The results of the white matter examination by DTI showed in general less significant changes with aging than the changes observed in the gray matter (see Table 2 and Fig. 5). DTI uses several indices to describe the diffusivity of water molecules in the tissue (FA, MD, L1, L2, L3). L1, 2 and 3 are perpendicular axes (L1 axial, L2 and L3 radial) describing directional diffusivity in a 3D space.

In the part of the auditory pathway from the IC to HG (AP) with the threshold set at 10%, an increasing trend with age, which was more pronounced on the right side, was present in the L1 variable.

More trends were observed in the ROI of the white matter under HG in elderly subjects – the L1 values on the left side were lower than those on the right side, and the trend was pronounced mainly in the elderly groups. Mean diffusivity showed a decreasing trend on the left side with age. A trend toward an increase of AvgL2L3 accompanying a deterioration of hearing was observed.

DISCUSSION

The aim of our study was to investigate morphometric changes occurring in the auditory cortex and in the central part of the auditory pathway in aging subjects suffering from sensorineural hearing loss – presbycusis. Therefore, there were two variables in our study: age and the state of hearing. Our subjects were divided into three groups, i.e. YC, MP and EP, and the effect of age was evaluated by comparing YC with MP and the effect of hearing loss by comparing MP with EP. The third variable investigated was lateralization, which was based on a comparison of the changes in the left and right hemispheres.

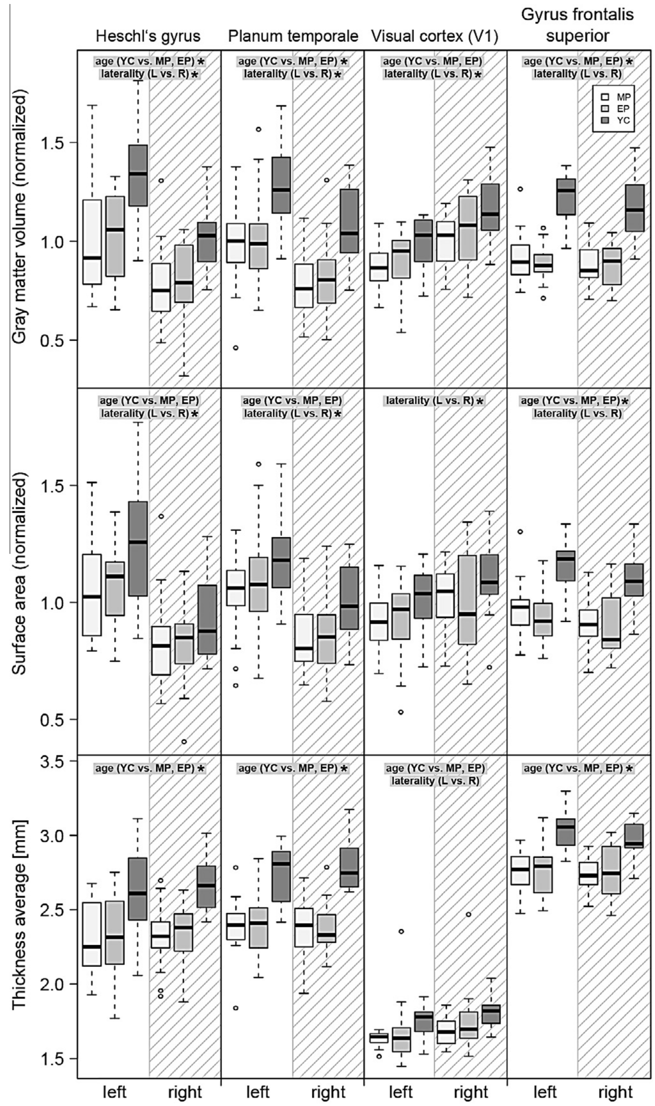

Fig. 4. Boxplots showing a comparison of the gray matter morphometric parameters (gray matter volume, normalized gyral surface area and the average thickness of the gray matter) for four areas: Heschl's gyrus, planum temporale, primary visual cortex and gyrus frontalis superior in the YC, MP and EP groups. Gray matter volume and gyral surface area values are normalized to their grand mean value across the corresponding anatomical area for the convenience of graphical display. The significance (the modeled effects) of age, laterality factors, or their interaction (age vs. laterality) is marked in each section of the graph (n.s. means no factor was significant; the asterisk denotes a significant effect under the conservative Bonferroni correction; the gray shading denotes descriptive uncorrected p-values (value 0.000 corresponds to $p < 0.001$). The central line of the box represents the median, while the upper and lower borders of the box represent the 75% and 25% quartiles. The upper whisker is drawn at the value of the largest data point with a value lower than the 75% quartile + 1.5 times the interquartile range (IQR). The lower whisker is drawn at the value of smallest data point with a value higher than the 25% quartile − 1.5 times the IQR. Individual data points with values higher than the 75% quartile + 1.5 times the IQR and data with values lower than the 25% quartile − 1.5 times the IQR are marked by circles. The IQR is defined as the difference between the 75% and 25% quartile.

The assessment of auditory system function in individual subjects was based on pure tone audiometry, which confirmed hypofunction of the auditory periphery in the MP and EP groups, and the central component of hearing loss was expressed by a deterioration of speech understanding. The elevation of hearing thresholds at frequencies above 1 kHz, which is a typical sign of presbycusis (Schuknecht and Gacek, 1993; Mazelová et al., 2003), was confirmed in all elderly subjects. The average hearing threshold of the MP group was within the physiological range or only a few dB below the range up to 8 kHz and therefore comparable with the YC, while a fast decline above 1 kHz was characteristic of the EP hearing thresholds. The observed deterioration of speech understanding is commonly used for describing the central component of presbycusis (Pichora-Fuller and Souza, 2003).

Gray matter

In agreement with the literature (Guo et al., 2008; Tyler et al., 2010; Bouma and Gootjes, 2011; Bonner and Grossman, 2012; Shafto et al., 2012) and with the

Table 2. P-values of the modeled effects for DTI indices. The asterisk denotes a significant effect under the conservative Bonferroni correction controlling the family-wise error rate among all the morphology effects hypothesis tests at 5% (adjusted threshold padjust = 0.05/60 = ∼0.0008). The gray shading highlights all *p*-values lower than 0.05, corresponding to uncorrected testing

Auditory pathway	Hearing	Age	Laterality	Hearing vs. laterality	Age vs. laterality
FA	0.4221	0.2585	0.8463	0.6891	0.9239
MD	0.8959	0.0599	0.1407	0.139	0.061
L1	0.6208	0.035	0.1179	0.1553	0.0253
AvgL2L3	0.5836	0.1982	0.2737	0.2441	0.211
White matter under Heschl's gyrus					
FA	0.3619	0.084	0.1767	0.9014	0.8603
MD	0.0675	0.0733	0.098	0.4093	0.0183
L1	0.3283	0.3624	0.0015	0.2789	0.0099
AvgL2L3	0.0377	0.0392	0.7163	0.6224	0.0775

results of our previous study based on MR spectroscopy (Profant et al., 2013), we observed in the auditory cortex of elderly subjects clear signs of atrophy of the gray matter expressed as a decreased volume of Heschl's gyrus and the planum temporale of these gyri and a decreased thickness of the gray matter present there. Although the presence of deficits at the level of the auditory periphery and the recorded morphometric changes may suggest an influence of the peripheral deficit on the AC morphology, this is not necessarily true. First, in congenitally deaf patients at age 30, there are no gray matter volume changes in the AC (Penhune et al., 2003). This is surprising because of the absence of natural peripheral input. One of the arguments is that the deafness is, in this case, compensated for by other sensory stimuli, most naturally by the visual and motor stimulation used in sign language, and that the functional reorganization of the AC is a result of their processing (Petitto et al., 2000; Newman and Twieg, 2001). Our findings of minimal differences in the morphometric parameters of HG and PT between both aged groups are in agreement with the findings in deaf subjects and thus support the theory that sensory deprivation is insufficient to cause morphometric changes in the gray matter.

Similar age-related changes in the morphometric parameters with an expressed decrease in the gray matter volume were found in both elderly groups, but no differences between them were observed in the GFS. This gyrus is considered to be involved in working memory contributing to higher cognitive functions (du Boisgueheneuc et al., 2006). Working memory is especially important in the processing of speech in the elderly, in whom it is considered to compensate for hearing loss by an increased listening effort (Lunner et al., 2009) and better use of semantic and episodic memory (Tulving, 2002; Stenfelt and Ronnberg, 2009). Although enhanced functional activation of the prefrontal cortex has been described in hearing loss (Wong et al., 2010) and in the elderly population in general (Park and Reuter-Lorenz, 2009; Vermeij et al., 2012), we were not able to confirm such enhancement at the level of morphometric changes of the gray matter. Another reason for adding GFS into our analysis was its

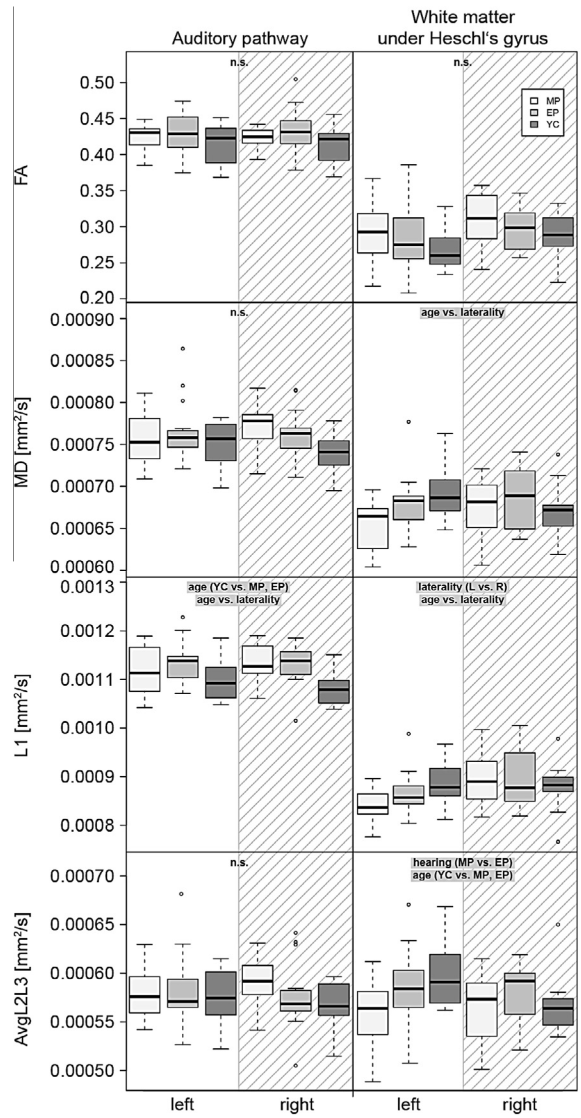

Fig. 5. Boxplots showing a comparison of the DTI parameters (FA, MD, L1, AvgL2L3) for two white matter regions: the auditory pathway from the IC to Heschl's gyrus (AP) and the white matter ROI under Heschl's gyrus. The significance (the modeled effects) of age, lateralization, hearing or the interaction of age and laterality (age vs. laterality) is marked in each section of the graph. For further descriptive details see the legend of Fig. 4.

non-sensory character and the size of the region, which provides more detailed changes and a better concordance index (Destrieux et al., 2010).

All three previously discussed cortical areas are related to hearing and speech, therefore the V1 region of the visual cortex was chosen as a control. In the gray matter volume and average thickness of the gray matter, the V1 results are comparable with those from the AC and GFS. However, a significant effect of age is missing in the V1, although a trend is present.

The third variable examined in our experiments was the effect of lateralization. In principle, the extent of cortical activation by sound is larger in the left than in the right hemisphere. In most people the left auditory cortex is dominant for the processing of speech and the temporal parameters of sound, whereas the right auditory cortex is involved in the processing of the spectral parameters of sound, frequency modulation and the processing of musical signals (Tramo et al., 2005; Firszt et al., 2006; Schirmer et al., 2012). The difference in the roles of the left and right auditory cortices in the processing of different parameters of sound signals is possible to observe already in mammals such as the laboratory rat (Rybalko et al., 2006, 2010). These functional differences also have their morphometric counterparts. The enlargement of the left PT is considered to correspond with speech processing by the left AC (HG + PT) (Toga and Thompson, 2003). A reduction of leftward asymmetry is present in dyslexic individuals (Heiervang et al., 2000), with impaired phonological decoding and difficulty in the processing of fast temporal information (Fitch et al., 1997; Morris et al., 1998). Our data show preserved asymmetry with aging with a larger left AC in terms of the gray matter volume and surface area, however not in cortical thickness. This asymmetry was not influenced in elderly subjects by the level of hearing loss.

The opposite asymmetry in the visual cortex, i.e. a dominant right hemisphere in terms of gray matter volume and surface area, corresponds with the data from the literature (Goldberg et al., 2013), which demonstrate, e.g., a much larger volume in the superior occipital gyrus on the right side.

White matter

The white matter was examined by DTI, which was used to detect changes in previously selected ROIs: the central part of the auditory pathway above the IC and in the white matter mask under HG. Since one of the probable components of presbycusis is cognitive decline with an expected degradation of neuronal networks, DTI seem to be the proper tool for detecting microstructural changes in the auditory pathway, which gives it an edge over classic volume-metric studies (Madden et al., 2009).

Our results suggest that in the part of the auditory pathway between the IC and the white matter under HG, L1 tends to increase with age. An L1 increase is, in general, considered to be a mark of intrinsic neuronal degradation and morphologic changes of neuronal fibers (Lin et al., 2008). A change of MD during aging, as described in human callosal fibers (Aboitiz et al., 1996), generally represents a disturbance of the white matter microstructure. We did not find a significant change of MD in the AP of aging subjects compared to YC.

Our data do not show significant change in FA values in the auditory pathway, which might be surprising in comparison with previous findings in the aged population (Pfefferbaum et al., 2000). However, the previously described changes in FA were found in structures with densely packed white matter fibers, such as the corpus callosum and centrum semiovale. An increase in FA in the auditory tract was previously described in the IC by (Lutz et al., 2007); however, since the IC predominantly contains gray matter, it is difficult to select purely the white matter part of the IC. (Chang et al., 2004) showed a decrease in FA in patients with sensorineural hearing loss (SNHL), whereas only a minimal change in FA was observed in our study. Our finding is in agreement with the results of Husain et al. (2011), who showed minimal subcortical changes in patients with SNHL and SNHL with tinnitus. The complete lack of sensory stimulation in prelingually deaf patients is associated with decreased FA and increased MD in the HG, STG and the splenium of the corpus callosum (Miao et al., 2013). The discrepancy in the effect of SNHL and presbycusis can be explained by the different effect on the auditory pathway. Idiopathic SNHL (Lin et al., 2008) generally affects the auditory system in a different time frame than presbycusis. In most cases it has a sudden onset, with an immediate effect on supracochlear structures, whereas presbycusis represents a slowly progressing long-term process. We can assume that there would be a degree of adaptation in elderly with presbycusis, which might explain the lack of FA changes in our subjects compared to more acute types of SNHL. However, the duration of the hearing loss in our elderly patients is unknown, therefore this is purely a conjecture. The most common model of acute SNHL in animals is represented by noise trauma. The results of animal experiments after noise trauma at the levels of the IC and MGB showed a significant loss (around 30%) of cell density (Groschel et al., 2010), whereas the overall decrease in the neuronal population of aging animals did not exceed 10% (Ouda and Syka, 2012) or was not significant (Helfert et al., 1999). Therefore, the expected effect after the acute onset of hearing loss described by DTI parameters would be an increase in MD and a decrease in FA in acute hearing loss, whereas presbycusis would show only minimal changes. Another difference is that in the studies by Chang et al. (2004) and Lin et al. (2008), the FA changes were present at the levels of the lateral lemniscus and IC, whereas we focused on the more central parts of the auditory pathway. Although minor changes of the white matter in the AP were recorded, the organizational scheme of the auditory pathway fibers, characterized by FA, was only minimally affected.

Overall, the white matter changes in the elderly population are mainly associated with cognitive decline and are pronounced in diseases such as multiple sclerosis and Alzheimer's disease (Madden et al., 2009). Although presbycusis does not fall under the umbrella of cognitive pathologies, there is a clear deficit in the processing of complex sounds, especially under altered acoustic conditions such as background noise or competing acoustical stimuli, which suggests a central component of the disorder (Humes et al., 2012). From the functional point of view, in the elderly population, cognitive decline and presbycusis are compensated for by the increased use of auditory associated areas, greater implementation of working memory located in the prefrontal cortex and increased involvement of the right AC (Sharp et al., 2006; Hickok and Poeppel, 2007; Radvansky and Dijkstra, 2007). Although, in our study we did not focus on intracortical tracts, one of the explanations for the changes recorded in WM_HG might be the expected reorganization toward strengthening the corticocortical tracts, which may compensate for the loss caused by the hypofunctional auditory pathway. To clarify the involvement of cognitive decline in central presbycusis, the employment of auditory cognitive tests, cognitive tests without the involvement of the auditory system and their association with MRI techniques (MR morphometry, fMRI) would be necessary. This combination of methods should be used in future research.

It is extremely difficult to explain the trends of the DTI indices in WM_HG, since the white matter in general loses the classical bundle organization below the level of cortex and the number of crossing and ‘‘kissing’’ fibers increases, therefore identifying a pathway and dividing the vectors into axial and radial is complicated (Alexander et al., 2001; Basser et al., 2002).

Our data do not support the previous finding of decreased FA in radiation under the AC in the elderly compared to young controls by Lutz et al. (2007). However, the overall lower FA in the WM_HG compared to the AP supports the notion of decreased white matter bundle organization below the cortex, which may mask such an effect. In our case In general, an increase of L2L3 accompanies demyelination (Madden et al., 2012). In our case a trend toward an increase of AvgL2L3 accompanying a deterioration of hearing was observed, and the boxplot also suggests a decreasing trend of AvgL2L3 on the left side with age.

The L1 and MD values change in a slightly different pattern in the WM_HG. We have detected a trend toward a decrease in MD and L1 with age predominantly on the left side, whereas on the right side the change is minimal. This would suggest that with increased age, the right side WM_HG is only minimally affected, which can be partially explained by the increased usage of the right AC in the elderly population (Balogová et al., 2013).

CONCLUSIONS

The study revealed age-related atrophy in the gray matter of the AC and neurons in the auditory pathway. Both methods showed that the high degree of hearing loss accompanying expressed presbycusis is not in principle sufficient to cause central changes detectable by MRI techniques. Large differences in laterality confirming the dominance of the left AC in the processing of auditory inputs were supported by our morphometric results, with only weak support provided by DTI. In general, the DTI results showed weaker effects compared to the gray matter morphometric changes.

In agreement with the previously reported data from MR spectroscopy in similar groups of subjects (Profant et al., 2013), the morphometric changes in the gray and white matter were predominantly caused by aging and were probably not influenced by the degree of hearing loss due to presbycusis. Our findings are different from the previously reported changes in the central auditory system produced by different types of SNHL, which is probably caused by a long-term adaptation of the auditory system in the processing of acoustical signals in the elderly.

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