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Reduced volume of Heschl's gyrus in tinnitus

Peter Schneider [a,b,*], Martin Andermann [a], Martina Wengenroth [b], Rainer Goebel [c], Herta Flor [a,*], André Rupp [d], Eugen Diesch [a,*]

[a] Department of Clinical and Cognitive Neuroscience, Central Institute of Mental Health, University of Heidelberg, J5, 68159 Mannheim, Germany
[b] Department of Neuroradiology, University of Heidelberg Medical School, INF 400, 69120 Heidelberg, Germany
[c] Department of Cognitive Neuroscience, Faculty of Psychology, Universiteit Maastricht, Postbus 616, 6200MD Maastricht, The Netherlands
[d] Department of Neurology, University of Heidelberg Medical School, INF 400, 69120 Heidelberg, Germany

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ABSTRACT

The neural basis of tinnitus is unknown. Recent neuroimaging studies point towards involvement of several cortical and subcortical regions. Here we demonstrate that tinnitus may be associated with structural changes in the auditory cortex. Using individual morphological segmentation, the medial partition of Heschl's gyrus (mHG) was studied in individuals with and without chronic tinnitus using magnetic resonance imaging. Both the tinnitus and the non-tinnitus group included musicians and non-musicians. Patients exhibited significantly smaller mHG gray matter volumes than controls. In unilateral tinnitus, this effect was almost exclusively seen in the hemisphere ipsilateral to the affected ear. In bilateral tinnitus, mHG volume was substantially reduced in both hemispheres. The tinnitus-related volume reduction was found across the full extent of mHG, not only in the high-frequency part usually most affected by hearing loss-induced deafferentation. However, there was also evidence for a relationship between volume reduction and hearing loss. Correlations between volume and hearing level depended on the subject group as well as the asymmetry of the hearing loss. The volume changes observed may represent antecedents or consequences of tinnitus and tinnitus-associated hearing loss and also raise the possibility that small cortical volume constitutes a vulnerability factor.

Introduction

Tinnitus is an auditory phantom sensation with ringing, hissing, or buzzing sounds (Jastreboff, 1990). Up to 17% of the adult population experience tinnitus at least occasionally (Hazell, 1990) and as many as 5–10% report unremitting tinnitus, with about 1–3% of the tinnitus sufferers experiencing interference with their lives (Baguley, 2002; Eggermont and Roberts, 2004). However, the underlying pathomechanism has not yet been identified.

As tinnitus often persists even subsequent to auditory nerve transsection (Jackler and Whinney, 2001; Jackson, 1985), processes in the central nervous system may play a major role in its development and maintenance (Bartels et al., 2007; Eggermont, 2005; Lockwood et al., 2002; Moller, 2003). Several neuroimaging studies employing magnetoencephalography (Diesch et al., 2004; Mühlnickel et al., 1998; Weisz et al., 2005; Weisz et al., 2007; Wienbruch et al., 2006), positron emission tomography (Andersson et al., 2000; Langguth et al., 2006; Lockwood et al., 2001; Plewnia et al., 2007), functional magnetic resonance imaging (Melcher et al., 2000; Smits et al., 2007) or repetitive transcranial magnetic stimulation (Folmer et al., 2006; De Ridder et al., 2005; Kleinjung et al., 2005; Plewnia et al., 2007) reported subcortical and cortical changes in tinnitus patients. Using the method of voxel-based morphometry (VBM, Ashburner and Friston, 2000), a recent volumetric magnetic resonance tomography studies demonstrated tinnitus-related structural changes in the subcallosal region including the nucleus accumbens and, within the auditory pathway, at the level of the medial geniculate (Mühlau et al., 2006). Volumetric effects were not reported for the auditory cortex. However, the supratemporal plane is a cortical region with rather complex convolutions, which are interindividually highly variable (Hackett et al., 2001; Leonard et al., 1998; Patterson et al., 2002; Schneider et al., 2005) and potentially too variable for VBM to unravel volumetric differences or changes. Volumetric differences may constitute vulnerability factors for tinnitus or, alternatively, reflect structural plasticity. The lateralization of tinnitus and hearing loss may constitute another problem. Perceptually, tinnitus may be perceived in the left ear, in the right ear, in both ears, or in the center of the head. Occurrence of tinnitus has been reported in individuals with little or without hearing loss in the conventionally tested frequency range up to 8 kHz and thresholds no worse than those of healthy controls in the high

* Corresponding authors. P. Schneider is to be contacted at Department of Neuroradiology, University of Heidelberg Medical School, INF 400, 69120 Heidelberg, Germany. H. Flor, Department of Clinical and Cognitive Neuroscience, Central Institute of Mental Health, University of Heidelberg, Square J5, 68159 Mannheim, Germany. E. Diesch, Department of Clinical and Cognitive Neuroscience, Central Institute of Mental Health, University of Heidelberg, Square J5, 68159 Mannheim, Germany.
E-mail addresses: peter.schneider@med.uni-heidelberg.de (P. Schneider), herta.flor@zi-mannheim.de (H. Flor), eugen.diesch@zi-mannheim.de (E. Diesch).

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frequency region between 8 and 18 kHz (McKee and Stephens, 1992) and 8 and 20 kHz (Barnea et al., 1990). However, in individuals with hearing loss these differences in the perceptual localization of tinnitus seem to be related to hearing loss asymmetries (Ochi et al., 2003; Nicolas-Puel et al., 2006; Van de Heyning et al., 2008). Furthermore, Melcher et al. (2000) reported an association of unilateral tinnitus with asymmetric activation in the inferior colliculus. Therefore, it may be prudent to separately consider the left and the right hemisphere when analyzing volumetric change in auditory cortex.

In the present study, a structural segmentation method that was tailored to the individual anatomy of the subject under investigation was used. Previous research using this approach has demonstrated a strong positive correlation of musical ability with Heschl's gyrus (HG) gray matter volume (Schneider et al., 2002; Schneider et al., 2005). We hypothesized that tinnitus may be associated with a potentially complicated pattern of altered mHG gray matter volume. First, chronic tinnitus is more likely to arise in older than in younger individuals (Baguley, 2002; Eggermont and Roberts, 2004) and age is associated with cortical and subcortical gray matter volume decrements (Bartzokis et al., 2001; Good et al., 2001; Raz et al., 2005; Zimmerman et al., 2006). Second, in analogy to chronic pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006) and fibromyalgia (Kuchinad et al., 2007), chronic tinnitus may be more likely to arise in the context of a degenerative process affecting mHG volume. Basta et al. (2005) reported gray matter volume reduction in the thalamus and auditory cortex of mice exposed to the kind of acoustic trauma that has been shown to induce tinnitus in hamsters (Heffner and Harrington, 2002). Thus, a degenerative process putatively leading to tinnitus may be age-related, related to hearing loss, or both. On the other hand, if volume loss may predispose towards tinnitus, then individuals with small gyri of Heschl may be more prone to develop tinnitus just as individuals with small hippocampi may be more likely to develop posttraumatic stress disorder after having lived through a traumatic event (Gilbertson et al., 2002). Furthermore, if musical training results in mHG enlargement (Gaser and Schlaug, 2003), musical training might even suppress tinnitus. Hence, musicians might be more resistant to developing tinnitus than non-musicians. On the other hand, one could argue that musicians should be more likely to develop tinnitus due to their permanent noise exposure to high-intensity sounds like amplified music, booming drum beats, clashing cymbals or blaring trumpets. However, recent psychometric studies suggest that musical performance does not pose an increased risk of hearing impairment or associated tinnitus for orchestral musicians (Lee et al., 2005). In either case, as musicians show larger HG volume than non-musicians (Schneider et al., 2002; Schneider et al., 2005), the response to the emergence of tinnitus may differ between musicians and non-musicians. Finally, since tinnitus is an auditory percept that in many cases is continuously present and often is attentively focused on, tinnitus may even induce volume increments, in analogy to training effects (Draganski et al., 2004; Boyke et al., 2008; Driemeyer et al., 2008), perhaps mediated by the gamma band component of the synchronized cortical hyperactivity that is characteristic of tinnitus (Eggermont, 2007; Weisz et al., 2007). Gamma band synchronization has been linked to attention, the formation of perceptual gestalts, and to memory (Kaiser and Lutzenberger, 2003). In this latter case in particular, even if hearing loss should primarily cause atrophic volume decrements, we would expect that it may ultimately trigger an opposing process resulting in volume increase.

Materials and methods

Sixty-one patients with chronic tinnitus and 45 controls participated in the study (for details see Table 1). Patients were included if they presented with chronic tonal or quasi-tonal tinnitus with a tinnitus frequency above 1 kHz. Tinnitus was considered chronic if its onset dated back six months or more. Individuals with noisiform or pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were excluded from the study in order to obtain a more homogeneous sample. Tinnitus was defined as chronic if it had lasted for at least six months. Controls did not present with either acute or chronic tinnitus. Participants were assigned to the musician group if they worked as professional musicians, earned a score of at least 25 on the Advanced Measures of Music Audiation (AMMA) test, a standardized test of musicality which is independent of musical expertise (Gordon, 1989, Gordon, 1998), or both. Patients and controls were recruited through press advertisements and flyers. Some musicians, both patients and controls, were recruited by directly contacting orchestra ensembles. All subjects gave written informed consent following procedures approved by the ethics committee of the University of Heidelberg.

Table 1
Subject characteristics, psychoacoustic test results, and TQ tinnitus questionnaire scores

	NN	MN	NT	MT
Subject characteristics/group				
N [all (female)]	16 (11)	29 (12)	35 (10)	26 (10)
Age in years [mean (SEM)]	40.8 (3.1)	37.7 (1.9)	49.3 (1.9)	39.4 (2.5)
Handedness [*N* left-handed]	1	0	1	5
Tinnitus onset [years (SEM)]	–	–	10.6 (1.7)	10.9 (2.7)
Psychoacoustics				
Tinnitus location: *N* [LE/BE/RE]	–	–	13/9/13	5/8/13
Tinnitus frequency [kHz (SEM)]	–	–	7.7 (0.5)	9.1 (1.0)
Tinnitus minimum masking level [dB]	–	–	17.8 (4.5)	26.1 (6.9)
RE hearing loss dB HL [LE/BE/RE][a]			24(6)/47(8)/50 (5)	14(8)/17(8)/35 (9)
LE hearing loss dB HL [LE/BE/RE][a]			36(5)/51(9)/42 (4)	14(9)/22(7)/26 (7)
N [hearing loss ≤/>15 dB HL]	11/4	18/9	2/32	14/12
AMMA tonal score	21.8 (0.64)	31.2 (0.89)	20.8 (0.5)	29.4 (0.7)
Goebel Hiller questionnaire				
Total score	–	–	32.2 (3.7)	14.2 (2.1)
Tinnitus intrusiveness	–	–	9.4 (0.7)	4.3 (0.6)
Cognitive and emotional distress	–	–	15.2 (2.0)	6.2 (1.2)
Somatic complaints	–	–	1.2 (0.3)	0.5 (0.2)
Auditory and perceptual difficulties	–	–	4.6 (0.7)	2.4 (0.6)
Sleep disturbances	–	–	2.0 (0.3)	1.0 (0.3)

In parentheses: number of females in line 1, SEM otherwise. NN: non-musicians without tinnitus, MN: musicians without tinnitus, NT: non-musicians with tinnitus, MT: musicians with tinnitus. LE: left ear, RE: right ear, BE: both ears. LH: left hemisphere, RH: right hemisphere. AMMA: advanced measures of music audiation test.
[a] Right ear hearing loss, left ear hearing loss in dB HL (hearing level) as measured at the tinnitus frequency for perceptual tinnitus locations LE, BE, and RE.

Twenty-six of the 61 patients and 29 of the 45 controls were musicians. Group age means were 40.8(3.1) years for non-musicians without tinnitus (group NN), 37.7(1.9) years for musicians without tinnitus (group MN), 49.3(1.9) years for non-musicians with tinnitus (group NT), and 39.4(2.5) years for musicians with tinnitus (group MT). The time since onset of the tinnitus was 10.6 (1.7) years in group NT and 10.9 (2.7) years in group MT. In group NT, tinnitus was lateralized to the left ear in 13 and lateralized to the right ear in another 13 patients. Tinnitus was bilateral or perceived in the middle of the head in 9 patients. In group MT, there were 5 left-sided, 13 right-sided, and 8 bilateral and central cases.

Subject characteristics are tabulated in Table 1. The groups differed significantly in age ($F[3,102]=6.5$, $p<0.0005$). Scheffé contrasts

($p<0.05$) showed that group NT was significantly older than groups MT and MN. Accordingly, age was entered as a covariate in all analyses of variance that were computed. There were no significant differences between the groups with regard to the proportion of males and females ($\chi^2(3)=6.5$, n.s.) or with regard to handedness (Fisher–Freeman–Halton test: $c(3)=5.3$, n.s.). Among tinnitus patients, musicians did not differ from non-musicians in the time since onset of the tinnitus ($F[1,47]=0.74$, n.s.).

All participants were investigated for the extent of hearing loss using pure-tone audiograms. Tinnitus patients were tested for the frequency and the minimum masking level of their tinnitus. They were interviewed as to their perceived location of the tinnitus. Perceived tinnitus location was coded on a five-point scale (exclusively in the left ear, predominantly in the left ear, in both ears, or centralized in the middle of the head, predominantly in the right ear, exclusively in the right ear). Patients were also given the German version of the Tinnitus Questionnaire (TQ,Hallam et al., 1988, Hallam, 1996) published by Goebel and Hiller (Goebel and Hiller, 1994; Goebel and Hiller, 1998).

For the audiometric and psychoacoustic tests stimuli were presented monaurally using a Hammerfall DSP Multiface System and closed dynamic headphones (Sennheiser HDA 200) designed for extended high frequency testing. The absolute threshold of hearing was determined for twelve frequencies between 0.125 kHz and 15 kHz using a computer-based standard three-interval forced choice procedure implemented on the basis of the MATLAB AFC software package developed at the University of Oldenburg (Ewert and Dau, 2004). Both the tones and the intervals between the tones were 500 ms in duration; the tones had 20 ms onset and offset ramps.

Threshold values were obtained in dB full scale (dB FS) and then rescaled in terms of dB hearing level (dB HL). Initially, the rescaling coefficients were obtained from a subgroup of 30 subjects for whom clinical audiograms with extended frequency range up to 10 kHz were available (Audiomaster CA 540/1, Hortmann Neuro-Otometrie, a division of GN Otometrics GmbH and Co KG, Neckartenzlingen, Germany). The rescaling coefficient for 15 kHz was obtained by piecewise cubic extrapolation from this set of rescaling coefficients using the matlab interp1 procedure with the "cubic" and "extrap" options. This is feasible because the frequency response both of the Hammerfall DSP Multiface and the Sennheiser HDA 200 is linear and flat between 10 and 16 kHz. When the test system was calibrated to deliver measurements scaled in dB sound pressure level (dB SPL) for the frequency range between 0.125 kHz and 10 kHz (setup: Brüel and Kjaer type 2231 sound level meter coupled with a Brüel and Kjaer type 4152 artificial ear and a Brüel and Kjaer type 4930 artificial mastoid) and the dB HL values were calculated from the calibrated dB SPL values using the IEC 318 correction, the mean difference between these and our previously obtained dB HL values was 2.9 dB (1.2 dB).

The frequencies tested were spaced equidistantly on the Bark scale (Zwicker, 1961, Zwicker and Terhardt, 1980), with the exception that spacing was twice as large for the six lower (0.125 … 2.87 kHz) than for the six higher frequencies (3.67 … 15.0 kHz). Following the criterion used in the selection of tinnitus patients, a (quasi-) tonal tinnitus with a tinnitus frequency above 1 kHz, four summary indices of hearing loss were computed by averaging across frequencies, i.e. right and left ear low frequency (125 Hz … 746 Hz) and high frequency (1.183 kHz … 15 kHz) hearing loss. Additionally, left (right) ear hearing loss at the tinnitus frequency was computed by interpolating between the hearing loss values actually measured for the left (right) ear that were closest to the tinnitus frequency on the frequency axis. For each of the twelve frequencies tested an index of hearing loss asymmetry was computed in terms of the difference between right ear (RE) and left ear (LE) hearing loss (HL) scaled in dB: $\delta_{HL}=HL_{RE}-HL_{LE}$ [dB]. Because of division-by-zero problems, the raw difference score $HL_{RE}-HL_{LE}$ rather than the standardized difference score $(HL_{RE}-HL_{LE})/(HL_{RE}+HL_{LE})$ was used and $HL_{RE}+HL_{LE}$ was entered as a covariate into statistical procedures that included the raw difference score as a variable.

The tinnitus frequency was determined by a recursive two-interval forced-choice procedure (Diesch et al., 2004), a reliable measure of tinnitus frequency (Henry et al., 2000, Henry and Meikle, 2000). The frequency interval of interest was bisected into two subintervals that were equal on the Bark scale and thus perceptually equivalent. For both the low and the high frequency subinterval it was determined by repeated testing whether the tinnitus was more similar to its low or its high frequency end. Depending on the outcome, bisection and two-interval forced-choice testing were reapplied to the low subinterval, the high subinterval, or rather a new middle interval that was bound by the midpoints of the low and the high subinterval. The procedure was terminated if responses to repeated tests within a subinterval fell below a preset level of consistency or if the results from the low and the high subinterval were inconsistent. Patients were included in the study if and only if they were able to reliably home in on their tinnitus or a salient tonal component thereof.

For the measurement of the minimal masking level of the tinnitus (TMML), a narrow-band "low-noise noise" (Dau et al., 1999; Kohlrausch et al., 1997) with a relative bandwidth of 0.7 critical bands was presented as a masker stimulus. Low-noise noise exhibits a smooth temporal envelope without excessive peaks and troughs and thus lends itself optimally to the measurement of the tinnitus minimal masking level. The center frequency of the masker was equated with the tinnitus frequency. TMML was determined as the difference between the intensity level that was just sufficient for masking the tinnitus and the threshold intensity level at which the masker was just audible.

Tinnitus severity was measured using the German TQ version (Goebel and Hiller, 1994; Goebel and Hiller, 1998). This instrument includes several subscales: Intrusiveness of the tinnitus, cognitive and emotional distress, auditory and perceptual difficulties, sleep disturbances, and somatic complaints.

As summarized in Table 1, musicians with tinnitus did not differ from non-musicians with tinnitus with regard to the tinnitus frequency ($F[1,57]=0.80$, n.s.), the distribution of perceived tinnitus locations (Fisher–Freeman–Halton test: $c(4)=3.2$, n.s.), and the tinnitus minimum masking level ($F[1,39]=0.34$, n.s., regression on age: $F[1,39]=11.4$, $p<0.002$, with older subjects exhibiting lower tinnitus minimum masking levels). Musicians attained significantly lower scores than did non-musicians on the Goebel and Hiller (1994, 1998) tinnitus questionnaire ($F[1,45]=12.9$, $p<0.001$) and its subscales for "tinnitus intrusiveness" ($F[1,55]=21.6$, $p<0.0005$), "cognitive and emotional distress" ($F[1,55]=10.9$, $p<0.002$), and "somatic complaints" ($F[1,55]=5.9$, $p<0.05$). There was no significant group difference on the subscales of "auditory and perceptual difficulties" ($F[1,55]=2.6$, n.s.) and "sleep disturbances" ($F[1,55]=2.43$, n.s.). As expected, musicians earned significantly higher tonal AMMA scores than non-musicians ($F[1,78]=133.7$, $p<0.0005$), but the AMMA scores of tinnitus patients did not differ significantly from those of controls ($F[1,78]=3.3$, n.s.).

To obtain volumetric measures of the medial Heschl's gyri (mHG) of the left and the right hemisphere, the three-dimensional gray matter surface of individual auditory cortices was reconstructed from T1-weighted MRI data (Siemens, Trio, 3 T, MPRAGE, 176 sagittal slices, slice thickness 1 mm, TR 1930 ms, TE 4.38 ms) after semi-automated segmentation by the BrainVoyager software program (Brainvoyager QX, version 1.8, Brain Innovation). The images were corrected for inhomogeneity, rotated in the direction of the anterior–posterior commissural line, and normalized by unfiltered transformation in Talairach space (Talairach and Tournoux, 1988). Using standard definitions of anatomical landmarks of the auditory cortex (Leonard et al., 1998; Morosan et al., 2001; Penhune et al., 1996; Penhune et al., 2003; Rademacher et al., 2001; Westbury et al., 1999), the sagittal MRI slices of individual auditory cortices were segmented along the

Sylvian fissure including the planum temporale (PT), Heschl's gyrus (HG), and the anterior supratemporal gyrus (aSTG) (Fig. 1). Prior to morphometric analysis, the HG was identified by the first complete Heschl sulcus (HS) as its posterior and the first transverse sulcus (FTS) as its anterior boundary (Morosan et al., 2001; Rademacher et al., 2001). The medial boundary of the HG was identified in terms of the line connecting the medial end of FTS to the medial end of the most anterior HS. The medial-to-lateral extent of mHG was defined by a fixed distance of 24 mm in order to confine the region of interest to the primary auditory cortex (PAC) and to fully include it. The distance chosen represents a compromise between the known average location of primary auditory cortex in the medial two-thirds of Heschl's gyrus and the known interindividual variability of its location (Hackett et al., 2001; (Leonard et al., 1998; Patterson et al., 2002; Schneider et al., 2005). Five major types of HG morphology were distinguished with respect to gyral duplications (Fig. 2, Table 2): presence (1) of a single HG, (2) of a HG with a common stem duplication reaching the lateral but not the medial end of HG, (3) a local intermediate sulcus (SI) reaching neither its medial nor its lateral end, (4) of a HG with a medial duplication, reaching the medial, not the lateral end (5) presence of a complete posterior duplication (PD) with a second, posterior HG (Schneider et al., 2005). In several rare cases, a multiple gyration with three or four transverse Heschl's gyri was observed. The medial and complete posterior duplications (cases 4 and 5), reaching both the medial end of mHG, were considered to be part of the planum temporale and were not included in the computation of mHG volume.

A cuboid-shaped region of interest was defined comprising the left and right auditory cortex in which the inclusion range of gray matter intensity values was calculated. The inclusion range of gray matter intensity values was derived from the intensity histograms of gray matter values: The half-side slope of gray matter peak distribution (i) towards cerebral spinal fluid and (ii) the saddle point between the gray and white matter peak was identified for each subject. All voxels within this inclusion range for gray matter intensities were marked and used for three-dimensional reconstruction. In both hemispheres, gray matter volumes of mHG were calculated in eight successive cross-sectional 3 mm-slices that were orientated perpendicularly to the major axis of the individual mHG. For each of the resulting eight homologous segment pairs, an index of volumetric asymmetry was computed in terms of the standardized difference between the right and the left hemisphere volume: $\delta_S=(V_{RH}-V_{LH})/(V_{RH}+V_{LH})$. Several summary indices of mHG volume and volume asymmetry were computed: right and left hemisphere postero-medial (segments 1 … 4) and antero-lateral (segments 5 … 8) volume, and postero-medial (segments 1 … 4) and antero-lateral (segments 5 … 8) volume asymmetry.

Results

Morphology and volumetry of Heschl's gyrus

As reported previously (Schneider et al., 2002, 2005), the 3D-reconstruction of individual auditory cortices revealed large variability with respect to size, gyration, and HG duplication. There were no significant group differences with respect to the distribution of single HGs, intermediate sulci, HGs with medial duplication, and complete HG duplications (left hemisphere: Fisher–Freeman–Halton $c(9)=13.1$, n.s., right hemisphere: Fisher–Freeman–Halton $c(9)=11.2$, n.s.). The mHG volume of the left hemisphere was larger than the mHG volume of the right hemisphere both for tinnitus patients ($\chi^2(3)=13.7$, $p<0.005$) and controls ($\chi^2(3)=9.7$, $p<0.025$). Tinnitus patients and controls showed comparable hemispheric asymmetries with respect to the frequency of HG duplications, i.e. a more frequent single HG in the left hemisphere (tinnitus patients: LH 39.3%, RH 19.7%, controls: LH 46.7%, RH 17.8%) and a more frequent intermediate sulcus (SI) and common stem duplication (CS) in the right hemisphere (see Table 2).

Fig. 3 and Table 3 present a conspectus of the gray matter volume data subdivided by tinnitus status, lateralization of perceived tinnitus location, musicality, and hearing status. Multivariate analysis of variance (MANOVA, with tinnitus status and musicality as grouping factors and hemisphere and volume segment as repeated measures factors showed that gray matter volume of the investigated medial part of Heschl's gyrus (mHG) was smaller for tinnitus patients than for healthy controls ($F[1,101]=15.9$, $p<0.0005$) and larger for musicians than for non-musicians ($F[1,101]=80.9$, $p<0.00001$). Volume was larger in the left than in the right hemisphere ($F[1,102]=50.5$, $p<0.00001$). More lateral segments were larger than more medial segments ($T^2[7,96]=9.7$, $p<0.00001$). This effect was stronger in the left than in the right hemisphere (segment × hemisphere: $T^2[7,96]=0.83$, $p<0.00001$) and

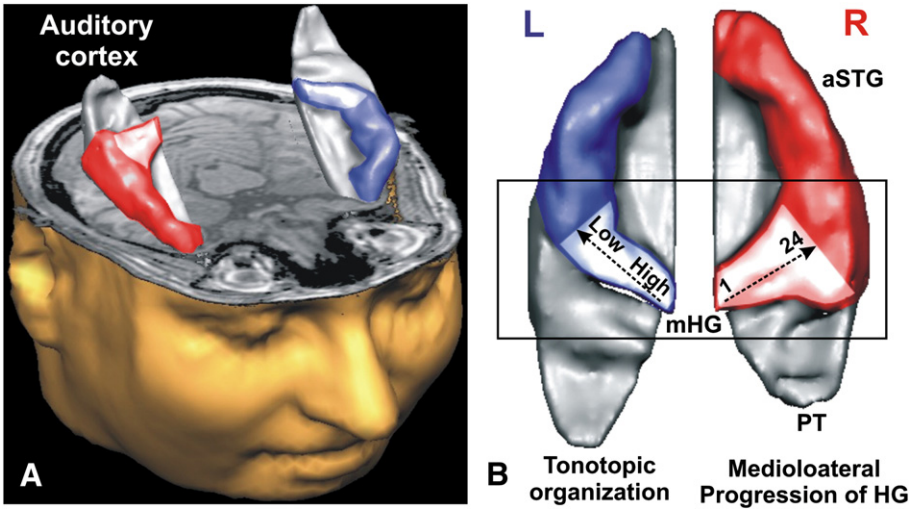

Fig. 1. Morphology of the auditory cortex (AC). (A) Individual 3D-reconstruction of the right and left AC, embedded in a transverse T1-weighted MRI section of the brain. (B) Top view of the segmented AC illustrating the anatomy of Heschl's gyrus (left: blue-colored, right: red-colored), the anterior part of the supratemporal gyrus (aSTG) and the planum temporale (PT) posterior to the HG. The posteromedial two-thirds of the HG are highlighted, comprising major parts of the primary auditory core fields. The arrow on the left indicates the gradient of the underlying tonotopic organization, ranging from high to low frequencies in medio-lateral direction. The arrow on the right indicates the 24 mm range along the medio-lateral extent of mHG for which the gray matter volume segments have been computed.

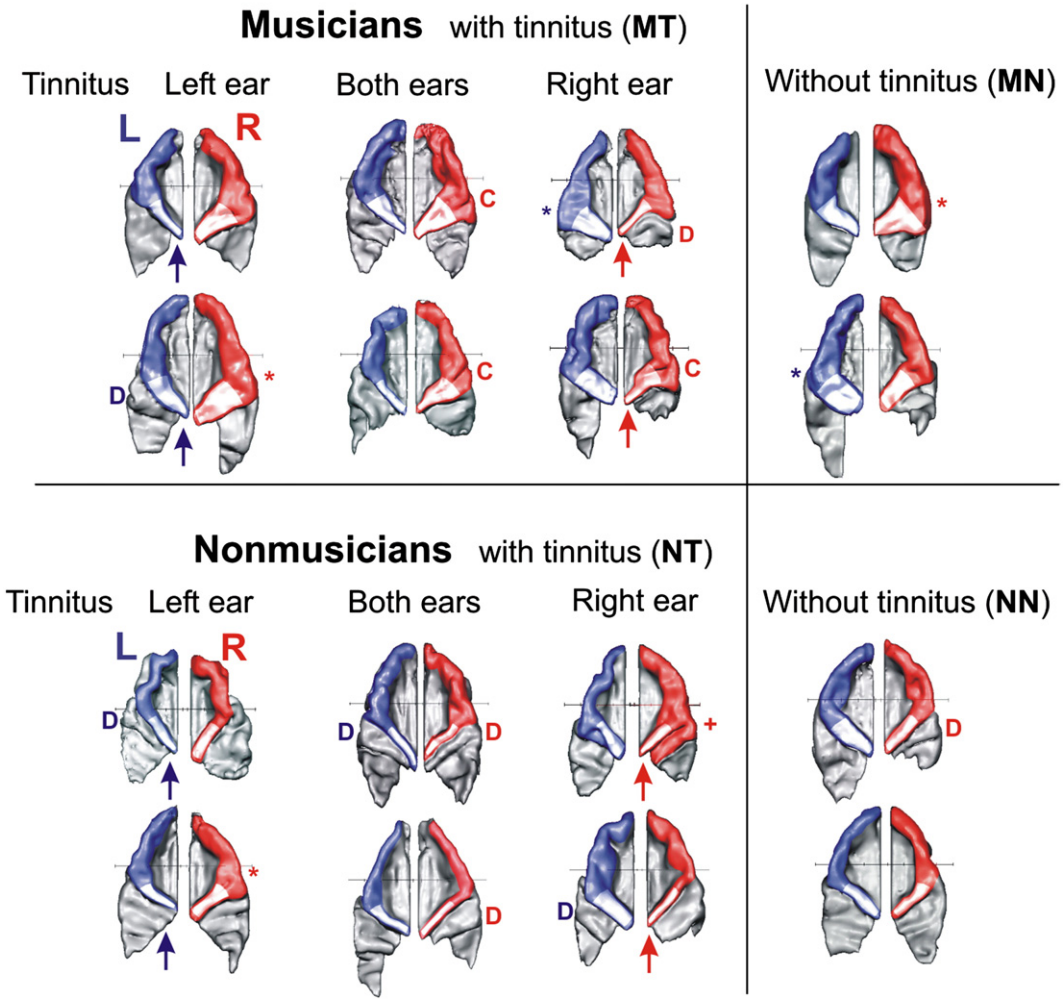

Fig. 2. Individual auditory cortex morphology of 16 representative subjects with the mHG partition of Heschl's gyrus highlighted in correspondence with the frame defined in Fig. 1. Arrows indicate the hemisphere ipsilateral to the tinnitus ear. A common stem duplication, characterized by a local Heschl sulcus reaching the lateral, however not the medial end, is marked by capital letter C. A local intermediate sulcus (SI), a small sulcus completely enclosed within the most anterior HG, is indicated by an asterisk (*). A medial duplication, characterized by a local Heschl sulcus reaching the medial, however not the lateral end, is indicated by a plus sign (+). A complete posterior duplication, separated from the anterior HG by a complete Heschl sulcus, is marked by capital letter D. In accordance with previous volumetric studies, musicians show significantly larger volumes of HG. Patients with unilateral tinnitus show a mHG volume reduction ipsilateral to the perceived tinnitus location. In patients with bilateral tinnitus, the mHG volume reduction was observed in both hemispheres. This effect was most prominent at the posteromedial end of mHG, sometimes culminating in a cone-shaped tapering.

stronger for musicians than for non-musicians (segment × musicality: $T^2[7,96]=0.64$, $p<0.00001$).

Among the correlations of right and left hemisphere total mHG volume with age, sex, handedness, body size, the four hearing loss indices (left and right ear, both low- and high-frequency), and, for tinnitus patients, time since onset of the tinnitus, those with age and some of those with hearing were significant. All of these latter correlations were negative, i.e. volume decreased with age and with hearing loss (see Table 4). The MANOVA analysis was rerun with age, sex, handedness, body size, and the hearing loss indices as covariates. Because of missing data, this reduced the sample size from 106 to 82 All main effects and interactions remained statistically significant (tinnitus status: $F[1,70]=8.5$, $p<0.005$, musicality: $F[1,70]=29.7$, $p<0.00001$, hemisphere: $F[1,78]=37.4$, $p<0.00001$, segment: $T^2[7,72]=7.9$, $p<0.00001$, segment × hemisphere: $T^2[7,72]=0.79$, $p<0.00001$, segment × musicality: $T^2[7,72]=0.53$, $p<0.00005$). None of the covariates was statistically significant.

Table 2
Frequency of HG duplications

Duplication/group		Single HG	SI	CS	MD	PD	Three HG
NN	Left	12	–	1	–	3	–
	Right	5	2	2	3	4	–
NT	Left	16	2	2	7	8	–
	Right	7	6	4	7	11	–
MN	Left	9	2	4	6	7	1
	Right	3	6	6	5	6	3
MT	Left	8	3	1	4	8	2
	Right	5	5	6	3	6	1
All	Left	45	7	8	17	26	3
	Right	20	19	18	18	27	4

SI: sulcus intermedius; CS: common stem duplication; MD: medial duplication; PD: complete posterior duplication.

For musicians, the present sample permitted a subdivision into subjects with normal hearing (high-frequency hearing level above 1 kHz ≤ 15 dB HL) and subjects with hearing impairment (high-frequency hearing level above 1 kHz > 15 dB HL). For non-musicians, this subdivision resulted in very small cell sizes. In a MANOVA with tinnitus and hearing status as grouping factors and hemisphere and volume segment as repeated measures factors, musicians with tinnitus showed smaller mHG volume than musicians without tinnitus ($F[1,51]=6.8$, $p<0.02$). Hearing impairment was not significant ($F[1,51]=1.9$, n.s.) and the interaction between tinnitus status and hearing impairment not either ($F[1,51]=0.24$, n.s.). As in the analysis of the total sample, the factors of hemisphere and segment and the

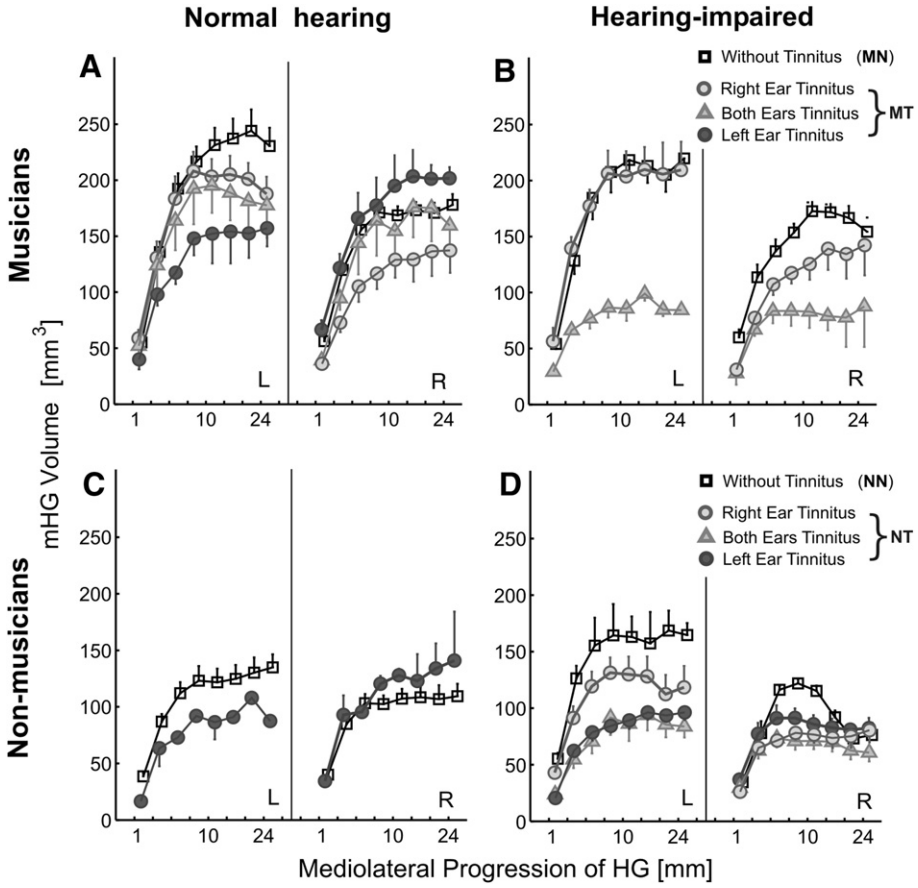

Fig. 3. Volume of mHG segments as a function of medio-lateral segment location. (Left) normally-hearing subjects (right) hearing-impaired subjects (top) musicians, (bottom) non-musicians. Subjects with normal hearing show hearing levels ≤15 dB HL (hearing level) above 1 kHz; subjects with hearing impairment show hearing levels >15 dB HL above 1 kHz. Dark circles: tinnitus patients with tinnitus lateralized to the left ear, light circles: tinnitus patients with tinnitus lateralized to the right ear, triangles: bilateral tinnitus, squares: healthy controls.

hemisphere-by-segment interaction were significant (hemisphere: $F[1,51]=21.2$, $p<0.00005$, segment: $T^2[7,45]=10.8$, $p<0.00001$, hemisphere-by-segment interaction: $T^2[7,45]=0.89$, $p<0.0001$). Significance levels were reduced, but the pattern of results was preserved, when age, sex, handedness, and body size were added as covariates (tinnitus status: $F[1,40]=5.6$, $p<0.025$; hearing impairment: $F[1,40]=0.005$, n.s.; tinnitus status by hearing impairment interaction: $F[1,40]=0.05$, n.s.; hemisphere: $F[1,44]=25.0$, $p<0.00005$, segment: $T^2[7,38]=12.1$, $p<0.00001$, hemisphere-by-segment interaction: $T^2[7,38]=1.18$, $p<0.0001$).

Volume reduction and lateralization of perceived tinnitus location

There was a distinct relationship between the asymmetry of mHG volume and perceived tinnitus location (Fig. 4, Table 3). The correlation attained significance for the seven most medial volume

Table 3
mHG volumes in mm^3

Volumetry/group		NN	MN	NT	MT
Left hemisphere mHG volume [mm^3] (SEM)	All	nh: 834 (64) hi: 1155 (112)	nh: 1506 (97) hi: 1531 (175)	nh: 618 (38) hi: 713 (40)	nh: 1236 (86) hi: 1201 (158)
	Tinnitus Left ear			627 (83)	952 (121)
	Tinnitus Both ears			629 (33)	1010 (109)
	Tinnitus Right ear			873 (87)	1448 (126)
Right hemisphere mHG volume [mm^3] (SEM)	All	nh: 736 (68) hi: 708 (24)	nh: 1168 (48) hi: 1206 (119)	nh: 869 (84) hi: 540 (28)	nh: 1034 (87) hi: 923 (92)
	Tinnitus Left ear			663 (56)	1299 (121)
	Tinnitus Both ears			439 (43)	888 (127)
	Tinnitus Right ear			543 (42)	901 (79)

SEM in parentheses. nh: normal hearing subjects (mean high frequency hearing level ≤15 dB HL), hi: hearing-impaired subjects (mean high frequency hearing level >15 dB HL). NN: non-musicians without tinnitus, MN: musicians without tinnitus, NT: non-musicians with tinnitus, MT: musicians with tinnitus. L: left ear, R: right ear, B: both ears. LH: left hemisphere, RH: right hemisphere.

Table 4
Correlations between the total mHG volume of the left (LH) and the right hemisphere (RH) with chronological age, left ear low frequency loss (LE LF loss), right ear low frequency loss (RE LF loss), left ear high frequency loss (LE HF loss), and right ear high frequency loss (RE HF loss)

Correlation	Age	LE LF loss	RE LF loss	LE HF loss	RE HF loss
LH mHG volume [mm^3] (SEM)	–,374**	–,258*	–,138	–,476**	–,398**
RH mHG volume [mm^3] (SEM)	–,363**	–,254*	–,121	–,407**	–,263**

Correlations marked by an asterisk are significant at the 0.01 level, correlations marked by two asterisks at the 0.0005 level.

segments in group NT (r=−0.37 … −0.68, p<0.05 … 0.0005, 8th segment r=−0.21, n.s.) and for all segments in group MT (r=−0.62 … −0.86, p<0.005 … 0.0005). mHG volume asymmetry, i.e. $\delta_S = (V_{RH}-V_{LH})/(V_{RH}+V_{LH})$, was larger in patients with tinnitus lateralized to the left ear (F[1,97]=34.6, p<0.0005) and smaller in patients with tinnitus lateralized to the right ear (F[1,97]=20.4, p<0.0005) compared to healthy controls. There was no difference between patients with bilateral or central tinnitus and controls (F[1,97]=0.04, n.s.). Overall, volume asymmetry was larger for postero-medial than for antero-lateral segments (T^2[7,92]=0.36, p<0.0005). In tinnitus lateralized to the right ear, the asymmetry difference relative to controls was larger for medial than for lateral segments (T^2[7,92]=0.21, p<0.02). Volume asymmetry was larger for musicians than for non-musicians (F[1,97]=7.7, p<0.01), in particular for the more medial segments (T^2[7,92]=0.16, p<0.05).

In patients with tinnitus lateralized to the right ear, volume of mHG was larger on the left than on the right hand side. Conversely, in patients with tinnitus on the left, volume of mHG was greater on the right than on the left hand side (Fig. 4). The significance of these asymmetries was further elucidated by the comparison of mHG volume reduction in unilateral left ear, unilateral right ear, and central/bilateral tinnitus. For this analysis, the left and right hemisphere mHG volume scores of the tinnitus patients were normalized using the means and standard deviations of volume scores of the respective control group, i.e. NN for NT and MN for MT. The standardized volume scores, which may be interpreted as volume reduction scores, were submitted to a MANOVA with tinnitus location (left, central/bilateral, right) as a grouping factor, and hemisphere (left, right) and segment (1 … 8) as repeated measures factors. To avoid small sample sizes, the analysis was pooled across musicians and nonmusicians. There was a significant interaction of hemisphere with segment (T^2[7,52]=0.85, p<0.0005), replicating the main analysis. The novel finding was that the interaction of tinnitus location with hemisphere was also significant (F[2,58]=37.9, p<0.00001). This result changed little with age, sex, handedness, body size and four hearing loss indices (left and right ear, both low- and high-frequency) introduced as covariates (F[2,50]=37.7, p<0.00001). In patients with tinnitus localized to the left ear, the volume reduction was larger in the left hemisphere than in the right. Conversely, if tinnitus was localized to the right ear, volume reduction was larger in the right hemisphere than in the left. Thus, it was the hemisphere ipsilateral to the ear affected by tinnitus that showed the largest volume reduction effects. Expressed in percentages, in unilateral tinnitus of the left side left hemisphere mHG volume was 65% and right hemisphere mHG volume was 95% of the left and right hemisphere mHG volume, respectively, in controls. For unilateral tinnitus of the right side, left hemisphere mHG volume was 102% and right hemisphere mHG volume was 76% of the left and right hemisphere mHG volume. For bilateral/central tinnitus, volume reduction was about the same in both hemispheres and comparable to the respective ipsilateral side of unilateral tinnitus.

The influence of hearing loss

Hearing loss (Fig. 5) was more pronounced in older than in younger subjects (age covariate: F[1,101]=55.7, p<0.0005) and more pronounced for tinnitus patients than for controls (F[1,101]=24.0, p<0.0005). The difference in hearing loss between patients and controls was larger for non-musicians than for musicians (tinnitus status×musicality status: F[1,101]=4.4, p<0.05). Hearing loss was larger for higher than for lower frequencies (T^2[11,92]=5.8, p<0.0005), in particular in the case of tinnitus patients (tinnitus status×frequency: T^2[11,92]=0.46, p<0.0005), and larger for non-musicians than musicians (tinnitus status×musicality status×frequency: T^2[11,92]=0.26, p<0.05). In group NT, the asymmetry of hearing loss measured at the tinnitus frequency was related to the perceived location of the tinnitus (r_{part}=0.57, p<0.001, with the average of the left ear and the right ear hearing loss, both measured at the tinnitus frequency, as a covariate). Thus, for group NT tinnitus

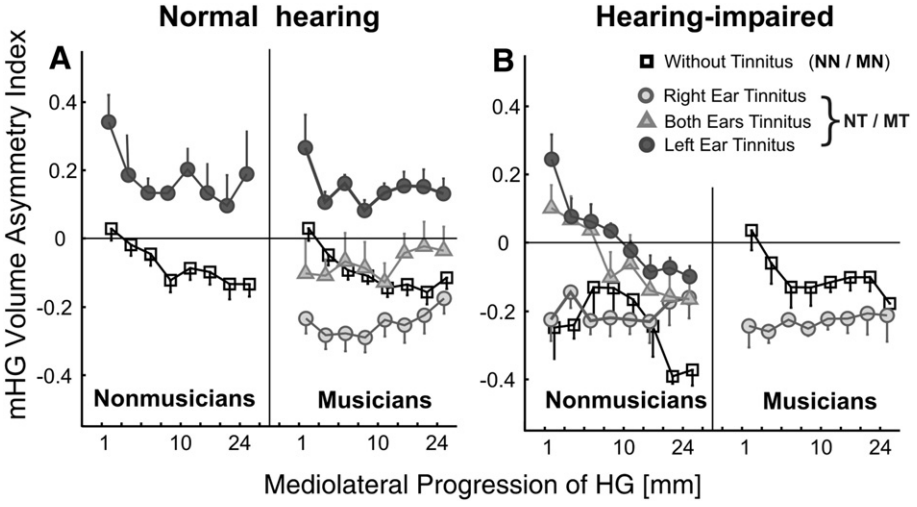

Fig. 4. Volume asymmetry, $\delta_S=(V_{RH}-V_{LH})/(V_{RH}+V_{LH})$, of mHG segments as a function of medio-lateral segment location for normally hearing subjects and hearing-impaired subjects, tinnitus patients and controls, musicians and non-musicians Positive index values indicate volume dominance of right hemisphere, negative index values volume dominance of the left hemisphere. Subjects with normal hearing show hearing levels ≤15 dB HL above 1 kHz; subjects with hearing impairment show hearing levels >15 dB HL above 1 kHz. Dark circles: tinnitus patients with tinnitus lateralized to the left ear, light circles: tinnitus patients with tinnitus lateralized to the right ear, triangles: bilateral tinnitus, squares: healthy controls.

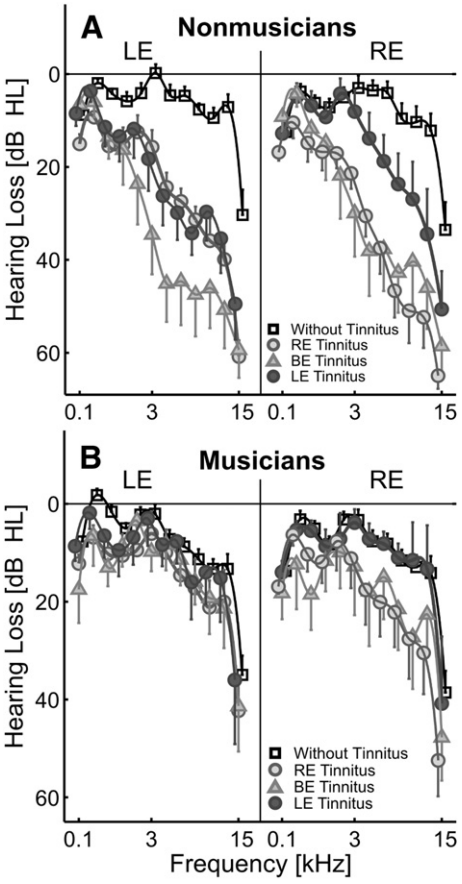

Fig. 5. Hearing loss in dB HL (hearing level) as a function of stimulus frequency. (Top) Non-musicians, (bottom) musicians. Dark circles: tinnitus patients with tinnitus lateralized to the left ear, light circles: tinnitus patients with tinnitus lateralized to the right ear, triangles: bilateral tinnitus, squares: healthy controls.

was lateralized perceptually to that ear that showed the larger extent of hearing loss at the tinnitus frequency. For group MT, however, this partial correlation fell short of significance (r_{part}=0.32, n.s).

The tinnitus minimum masking level and the TQ subscales TF_I ("tinnitus intrusiveness") and TF_A ("auditory and perceptual difficulties") exhibited significant correlations with high and low frequency hearing loss in the left and the right ear both for group MT and group NT. When the factor of age was partialled out, the correlations between TF_A and hearing loss remained significant, but only for group MT (low frequency, LE: r=0.65, p<0.01, RE: r=0.65, p<0.01; high frequency, LE: r=0.72, p<0.005, RE: r=0.64, p<0.01). None of the partial correlations, with age as a covariate, of left and right hemisphere postero-medial and antero-lateral mHG volume with tinnitus minimum masking level, the TQ global score, and the TQ subscale scores attained significance either in group NT or in group MT. Thus, although tinnitus may be etiologically linked to deafferentation induced by hearing loss (Eggermont, 2005; Eggermont and Roberts, 2004), in the wake of chronification there seems to be a certain measure of independence between tinnitus and hearing loss.

As shown in Table 4, total mHG volume, hearing loss, and age are interrelated. However, if age is partialled out, correlations between total mHG volume and hearing loss are considerably reduced (Fig. 6). In order to examine the relationship between mHG volume and hearing loss in more detail, partial correlations between left and right hemisphere postero-medial and antero-lateral mHG volume, on the one hand side, and left and right ear low and high frequency hearing loss, on the other hand side, were computed with age as the control variable. In groups NT and MT, the partial correlation with left and right ear hearing loss measured at the tinnitus frequency was also computed. Again, age served as a control variable. Thus, 16 partial correlations were computed for each of the control groups NN and MN, and 24 for each of the tinnitus groups NT and MT. The range of partial correlation coefficients was [−0.47 … 0.60] for group NN, [−0.37 … 0.21] for group MN, [−0.36 … 0.24] for group NT, and [−0.06 … 0.67] for group MT. After Bonferroni–Holmes correction, all correlations were insignificant for groups NN, MN, and NT. However, in group MT, the correlation between postero-medial left hemisphere volume (slices 1 … 4) and right ear hearing loss at the tinnitus frequency remained significant after Bonferroni–Holmes correction (r_{part}=0.67, p<0.001). This may be interpreted to suggest that in musicians with tinnitus hearing loss may be associated with an increase of cortical volume. From a meta-analytical perspective, whereas 18 of the 24 correlations in group NT were negative (sign test: p<0.025), only 2 were negative in group MT (sign test: p<0.00005). In groups NN and MN these proportions were 4/16 and 11/16, respectively (sign test: n.s.).

The partial correlation between the asymmetry of mHG volume and the asymmetry of hearing loss at the tinnitus frequency, with age and the average of the left ear and the right ear hearing loss, both measured at the tinnitus frequency, as control variables, was statistically significant for the volume summed across the postero-medial volume segments in group NT (r_{part}=−0.59, p<0.001), but not for the volume summed across the antero-lateral segments (r_{part}=−0.19, n.s.). It was insignificant both for postero-medial segments (r_{part}=

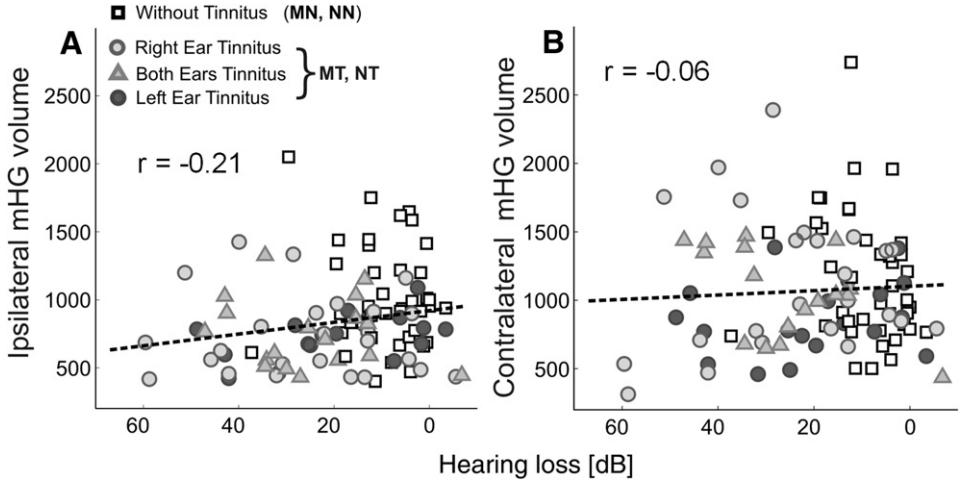

Fig. 6. Total mHG volume (across all segments) as a function of averaged (across both ears and all frequencies) hearing loss for the ipsilateral (left) and the contralateral (right) hemisphere with age partialled out.

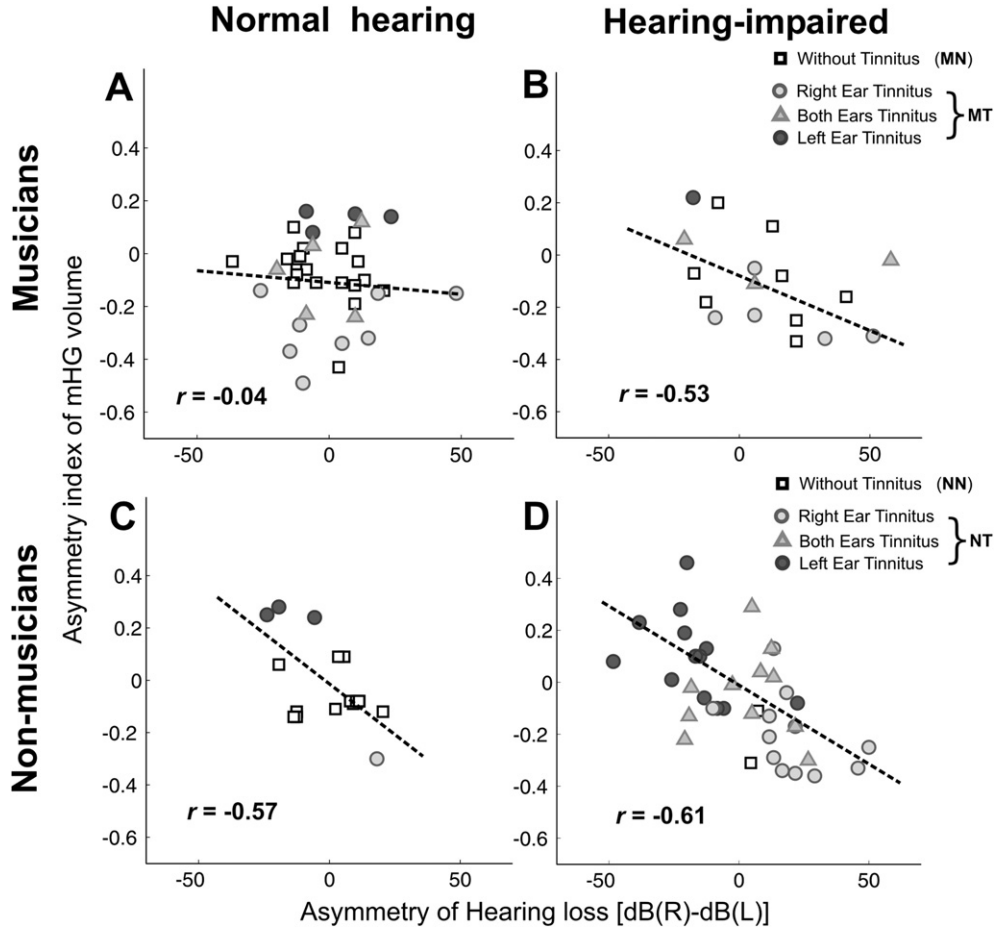

Fig. 7. Postero-medial mHG volume asymmetry, (R−L)/(R+L), as a function of maximum hearing loss asymmetry, R−L for (A) normal-hearing musicians, (B) hearing-impaired musicians, (C) normal-hearing non-musicians, and (D) hearing-impaired nonmusicians. Volume asymmetry was averaged across the postero-medial segments. Maximum hearing loss asymmetry was determined for right and left ear hearing loss values smoothed by a two-frequency moving average. The correlation coefficients displayed are partial correlations with age as covariate. Subjects with normal hearing show hearing levels ≤15 dB HL above 1 kHz; subjects with hearing impairment show hearing levels >15 dB HL above 1 kHz. Dark circles: tinnitus patients with tinnitus lateralized to the left ear, light circles: tinnitus patients with tinnitus lateralized to the right ear, triangles: bilateral tinnitus, squares: healthy controls.

−0.17, n.s.) and antero-lateral segments (r_{part}=−0.12, n.s.) in group MT, possibly because musicians with tinnitus lateralized to the left ear did not differ in left and right ear hearing loss measured at the tinnitus frequency (Table 1, lines 10 and 11). The correlation involving the postero-medial volume segments in group NT remained significant after Bonferroni–Holmes correction.

The partial correlations obtained between hearing loss and volume suggest that the correlation between hearing loss and volume asymmetry may depend on hearing status. Fig. 7 displays the interrelationship between average posterior-medial volume asymmetry and high-frequency hearing loss asymmetry for normal-hearing and hearing-impaired musicians and non-musicians. Maximum hearing loss asymmetry was determined for the right and left ear hearing loss values smoothed by a two-frequency moving average. The partial correlations were r_{part}=−0.04, n.s., for normal-hearing musicians, r_{part}=−0.53, $p<0.05$, for hearing-impaired musicians, r_{part}=−0.57, $p<0.05$, for normal-hearing non-musicians, and r_{part}=−0.61, $p<0.001$, for hearing-impaired non-musicians. The group of hearing-impaired non-musicians showed virtually complete separation between subjects with unilateral right ear and unilateral left ear tinnitus with the bilateral tinnitus subjects in between.

Discussion

Gray matter volume of the postero-medial partition of Heschl's gyrus (mHG) was smaller in individuals with tinnitus than in healthy controls. This volume difference was quite substantial in absolute terms and significant even after correction for age, gender, handedness, body size, and hearing loss. This finding was confirmed in the musicians-only analysis, where tinnitus status was significant, while the level of hearing impairment was not, suggesting that it is tinnitus rather than hearing impairment that is related to the volume reduction. In agreement with Penhune et al. (2003) and Dorsaint-Pierre et al. (2006), in the present study left hemisphere mHG was found larger in gray matter volume than right hemisphere mHG. This interhemispheric volume asymmetry was modulated by perceived tinnitus location. mHG volume asymmetry was strongest for the most postero-medial segments of mHG. In unilateral tinnitus, volume reduction was observed mainly in the hemisphere ipsilateral to the affected ear where it amounted to as much as 35 percentage points. The contralateral volume was largely preserved. In bilateral/central tinnitus, volume reduction was pronounced in both hemispheres. While, as observed previously for the lateral partition of Heschl's gyrus (Schneider et al., 2002, 2005), mHG volume was larger in musicians than in non-musicians, the volume difference between tinnitus patients and healthy controls appeared to be similar for musicians and non-musicians.

Cortical and subcortical volumetric changes

A previous volumetric study of tinnitus (Mühlau et al., 2006) reported an increase of gray matter volume concentration in the medial geniculate of the thalamus and volume decrease in the subcallosal region including the nucleus accumbens, but did not find

an effect at the level of the auditory cortex. The study employed the method of voxel-based morphometry (VBM, Ashburner and Friston, 2000). However, the high interindividual anatomical variability of the gyri of Heschl with respect to gyration and angulation may constitute a disadvantage for VBM approaches, because interindividual anatomical variability is likely to translate into regionally fluctuating statistical power to detect group differences (Tisserand et al., 2004). For instance, the hemisphere difference in HG gray matter volume in favor of the left hemisphere obtained in the present study has also been reported by Dorsaint-Pierre et al. (2006), but for individually guided volume measurements, not for VBM. Using diffusion tensor imaging (DTI), Yoo et al. (2006) analyzed white matter anisotropy in patients with tinnitus. Their preliminary results suggest the possible involvement of changes in white matter structures in tinnitus. However, controls were not included in this study.

Is volume reduction caused by hyperactivity-related gray matter atrophy?

Could the smaller gray matter mHG volume found in tinnitus represent gray matter loss brought about by atrophy or programmed cell death? In some respects tinnitus is similar to pain (Folmer et al., 2001, Moller, 2000). Tinnitus is associated with spontaneous hyperactivity and increased evoked response amplitudes in several structures of the auditory pathway including auditory cortex (Diesch et al., 2004; Eggermont and Roberts, 2004; Eggermont, 2005). It could be hypothesized that chronic hyperactivation might generate excitotoxic levels of glutamate receptor activation (Mattson, 2003) that are sufficient to generate the volumetric changes observed in the tinnitus sample investigated in this study. There have been several reports of cortical gray matter volume reduction in various pain conditions that have been interpreted as indicative of pathology-related atrophy. At the cortical level, chronic back pain has been shown to be associated with smaller gray matter volume of dorsolateral prefrontal cortex (Apkarian et al., 2004) and primary somatosensory cortex (Schmidt-Wilcke et al., 2006). In fibromyalgia, gray matter volume reduction has been found to be particularly pronounced in the medial frontal cortex, the left hemisphere insula, the middle and posterior cingulate gyrus, and the left parahippocampal gyrus (Kuchinad et al., 2007). Both Apkarian et al. (2004) and Kuchinad et al. (2007) have invoked atrophy secondary to excitotoxicity and/or as a consequence of the exposure to inflammatory agents, such as cytokines, as one possible explanation of volume reduction in terms of volume loss. However, the present data on the interrelationship of hearing loss and cortical volume are merely correlational. Furthermore, volumetric MRI data are ambiguous both with regard to the origin of group differences and the cellular and subcellular mechanisms underlying volume change (Weinberger and McClure, 2002). As has been argued for volumetric studies of pain conditions (Schmidt-Wilcke et al., 2006), longitudinal designs and appropriate treatment protocols will be needed to investigate whether all or part of the cortical volume reduction observed in tinnitus is produced by neurodegeneration rather than tissue shrinkage.

Does small mHG volume predate tinnitus rather than follow from tinnitus?

However, the observation that, in unilateral tinnitus, volume reduction effects are largely constrained to the hemisphere ipsilateral to the affected ear may present a problem to the idea that volumetric changes could be mediated by, for instance, excitotoxic levels of glutamate receptor activation purportedly generated by hyperactivity and hyperresponsivity of the afferent auditory pathway. Both hyperactivity and hyperresponsivity are not constrained to the ipsilateral projection. It is also important to note that in the present study there were no significant interactions involving the group variable of tinnitus status and the repeated-measurement variable of segment-within-mHG. The volume difference observed between patients and controls probably affects the full extent of primary auditory cortex, as primary auditory cortex tends to be located within the confines of the investigated partition of mHG (Galaburda and Sanides, 1980, Hackett et al., 2001, Rademacher et al., 1993). This renders it unlikely that the volume difference represents volume loss generated in the wake of deafferentation. If hearing loss were more pronounced for the higher frequencies, as it actually was, then, given the tonotopic organization of primary auditory cortex (Formisano et al., 2003), any volume-loss-by-deafferentation hypothesis would have to predict a significant mHG segment by tinnitus status interaction which did not obtain. If the processes that generate hyperactivation and tinnitus as sequelae of cochlear damage and hearing loss also generated mHG volume loss, a significant negative correlation between hearing loss and mHG volume would have to be expected. However, of all correlations computed between mHG volume and hearing loss, only the correlation of left hemisphere postero-medial mHG volume and right ear tinnitus-frequency hearing loss in group MT was statistically significant. And the sign of that correlation was positive. Similarly, a significant positive correlation would have to be expected between mHG volume asymmetry and hearing loss asymmetry. However, this correlation was significantly negative for non-musicians with tinnitus when hearing loss asymmetry at the tinnitus frequency was considered and it was significantly negative for non-musicians and hearing-impaired musicians. Therefore, it seems likely that the volume difference between patients and controls was present before the patients ever developed tinnitus. Small mHG volume may thus constitute a vulnerability factor. An individual with a small mHG may carry a higher risk to develop tinnitus in the wake of cochlear damage. Gray matter mHG volume was not significantly correlated with time-since-onset of the tinnitus, tinnitus minimum masking level, and the TQ subscale of tinnitus intrusiveness in tinnitus patients. Thus, although tinnitus may be etiologically linked to deafferentation induced by hearing loss (Eggermont, 2005; Eggermont and Roberts, 2004), after chronification there seems to be a certain measure of independence between tinnitus and hearing loss. The absence of these interrelationships is compatible with a vulnerability hypothesis. However, any form of vulnerability hypothesis can only be substantiated by studies involving longitudinal designs or studies of monozygotic twins.

Is unilateral tinnitus related to a lack of transcallosal inhibition?

In unilateral tinnitus, mHG volume reduction occurred almost exclusively ipsilateral to the affected ear. How can we make sense of this lateralization effect? If it were the hemisphere contralateral to the ear that the tinnitus is lateralized to that actually generated the sensation of tinnitus, then potentially because the reduced-size ipsilateral mHG does not generate the amount of tonic transcallosal inhibition necessary to prevent his from happening. Homotopic and heterotopic auditory cortical areas of the left and the right hemisphere are interconnected by the corpus callosum. Other than in vision and somatosensation where it is only the midline zone that features callosal fiber connections, in audition, callosal projections are distributed across the full extent of auditory cortex (Bamiou et al., 2007). While all callosal fibers originating from pyramidal cells are neurochemically excitatory, they may terminate on inhibitory interneurons. As a result, interhemispheric projections are both excitatory and inhibitory functionally (Bloom and Hynd, 2005). Under some conditions, the callosal influence is mainly inhibitory (Clarey et al., 1996; Kitzes and Doherty, 1994; Pluto et al., 2005; Tang et al., 2007). It is easier to observe transcallosal inhibition than transcallosal facilitation of primary auditory cortex single unit responses to auditory stimulation (Kitzes and Doherty, 1994). Transcallosal projections seem to combine focused facilitation with widespread lateral inhibition

(Tang et al., 2007). In the primary somatosensory cortex, widening of receptive fields, i.e. reduction of surround inhibition, has been observed in the wake of a reduction of the transcallosal influence (Clarey et al., 1996; Pluto et al., 2005). As there is an inverse relationship between callosal connectivity and hemispheric asymmetry (Aboitiz et al., 1992a, b; Dorion et al. 2000), a small mHG ipsilateral to the ear affected by tinnitus may generate a lesser amount of tonic inhibition of the contralateral mHG and thus facilitate the development of tinnitus-related activity. The positive correlation of left hemisphere postero-medial mHG volume with hearing loss, measured at the tinnitus frequency, in the right ear in the musician group, the negative correlation between postero-medial mHG volume asymmetry and the asymmetry of hearing loss at the tinnitus frequency observed in group NT, and the negative correlation between postero-medial mHG volume asymmetry and maximum hearing loss asymmetry in non-musicians and hearing impaired musicians are compatible with this hypothesis. To further explore the transcallosal inhibition hypothesis, it would be interesting to study the corpus callosum in patients with unilateral tinnitus.

Does unilateral tinnitus generate volume increments in the contralateral hemisphere?

The above scenario presumes that ipsilateral volume reduction actually predates the onset of tinnitus. While this remains a possibility, there may be alternatives. In acquired unilateral deafness, an enhancement of the amplitude of the ipsilateral cortical response, relative to the intact ear, to auditory stimulation of the intact ear has been observed using single unit recordings (Kitzes, 1984, Reale et al., 1987), magnetoencephalography (Li et al., 2006, Vasama and Makela, 1995), and functional magnetic resonance imaging (Firszt et al., 2006, Langers et al., 2005; Scheffler et al., 1998). For the present sample, the hemisphere contralateral to the tinnitus ear is the hemisphere that is ipsilateral to the audiometrically less impaired ear. It seems possible that cortical volume increments similar to the ones observed after environmental enrichment (Van et al., 2000) and sensorimotor training (Draganski et al., 2004; Boyke et al., 2008; Driemeyer et al., 2008) may manifest themselves in the wake of structural and functional changes of the afferent auditory pathway. In particular, the positive correlation of left hemisphere postero-medial mHG volume with the hearing loss, measured at the tinnitus frequency, in the right ear in the musician group, as well as the negative correlation between postero-medial volume asymmetry and asymmetry of hearing loss, again measured at the tinnitus frequency, in the non-musician group, and finally the negative correlation between postero-medial mHG volume asymmetry and maximum hearing loss asymmetry in non-musicians and in hearing-impaired musicians suggest that in tinnitus there may be frequency-selective and therefore place-selective volume increments that may take place in a prior setting of globally reduced volume and that are correlated with and possibly brought about by auditory deafferentation. In our sample, these volume increments assumed different forms for musicians and non-musicians which may mirror the fact that, at the tinnitus frequency, musicians with tinnitus lateralized to the left ear did not differ in hearing loss.

Does musical training protect against tinnitus?

Overall, musicians with tinnitus demonstrated lower TQ scores on the subscales of tinnitus intrusiveness, cognitive and emotional distress, and somatic complaints and a milder degree of high-frequency hearing loss than non-musicians with tinnitus. This raises the question if extensive musical training and practice may protect against tinnitus. Frequency discrimination training exerts an influence on frequency discrimination thresholds (Delhommeau et al., 2002; Demany, 1985; Irvine et al., 2000) and the tonotopic organization of primary auditory cortex (Polley et al., 2006; Rutkowski and Weinberger, 2005; Recanzone et al., 1993; but see Brown et al., 2004, for a negative finding). Frequency discrimination training may be beneficial in the treatment of tinnitus (Flor et al., 2004). Longitudinal studies may clarify if (i) reduced mHG volume constitutes a vulnerability factor and (ii) musical training and performance, even if accompanied with extensive exposure to high levels of sound density, may have a protective effect against auditory impairment.

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