nature neuroscience

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference

Peter Schneider[1], Vanessa Sluming[2,3], Neil Roberts[3], Michael Scherg[1], Rainer Goebel[4], Hans J Specht[5], H Günter Dosch[5], Stefan Bleeck[6], Christoph Stippich[1] & André Rupp[1]

The relative pitch of harmonic complex sounds, such as instrumental sounds, may be perceived by decoding either the fundamental pitch (f_0) or the spectral pitch (f_{SP}) of the stimuli. We classified a large cohort of 420 subjects including symphony orchestra musicians to be either f_0 or f_{SP} listeners, depending on the dominant perceptual mode. In a subgroup of 87 subjects, MRI (magnetic resonance imaging) and magnetoencephalography studies demonstrated a strong neural basis for both types of pitch perception irrespective of musical aptitude. Compared with f_0 listeners, f_{SP} listeners possessed a pronounced rightward, rather than leftward, asymmetry of gray matter volume and P50m activity within the pitch-sensitive lateral Heschl's gyrus. Our data link relative hemispheric lateralization with perceptual stimulus properties, whereas the absolute size of the Heschl's gyrus depends on musical aptitude.

Pitch perception is an essential prerequisite for understanding music and speech intonation. Although there is common agreement that the perceived pitch of harmonic complex tones like instrumental sounds or vowels in the singing voice is closely related to the fundamental frequency (f_0) of the sound spectrum, large individual differences in pitch and timbre perception challenge this one-to-one relationship[1,2]. In particular, if f_0 is not physically present, pitch is perceived either as the missing f_0 or as spectral pitch (f_{SP}), corresponding to the dominant perceptual mode (historically referred to as 'synthetic' versus 'analytic' pitch perception[3,4]).

At the cortical level, both frequency processing and pitch perception have been found to correlate with neural activity changes in the auditory cortex, related to different processing stages of hierarchically organized auditory subareas[5]. Physical stimulus properties such as periodicity[6], temporal regularity[7,8] and frequency spectrum[9] are encoded in both subcortical and cortical structures of the auditory ascending pathway. In primary auditory cortex, sound frequency is represented in mirror-symmetric tonotopic frequency maps[9,10] by spatiotemporal integration[11]. The more complex the stimuli and the processing tasks, ranging from pitch perception[12] to melody[7], timbre or tonality[13] processing, the more lateral and anterior are the main peaks of activation in Heschl's gyrus (HG) and anterior supratemporal gyrus (aSTG)[13–16]. Furthermore, the representation of pitch as a perceptual, rather than physical, stimulus property was found to correlate with neural activity changes in the non-primary auditory cortex[15]. Consistent with this finding, numerous functional imaging studies point to the existence of a 'pitch processing center'[12] immediately anterolateral to primary auditory cortex within the lateral Heschl's gyrus (lHG), subserving the processing of fixed pitch[16], pitch chroma[17], pitch salience[15], pitch direction[18], pitch sequences[19] and lively pitch[20].

Both relative hemispheric asymmetries[21–26] and the absolute magnitude of the neural auditory cortex substrate[27] are important in enabling understanding of how brain structure maps with the observed functional specialization. In particular, recent functional imaging studies show a relative left-hemispheric specialization for rapid temporal processing[23,25], whereas right auditory cortex shows a stronger sensitivity for spectral processing[23] and a slower temporal processing mode[25]. Motivated by these findings of asymmetry and strong mutual correlations between early auditory evoked activity, anatomical size and behavioral predisposition in the anteromedial portion of HG[27], we hypothesize here that f_0 versus f_{SP} perception may serve as a predictor reflecting both functional and structural aspects of the pitch-sensitive areas in lHG. The main purpose of this study was to investigate (i) individual psychometric differences in f_0 and f_{SP} perception in relation to musical aptitude, (ii) the neural basis for type of pitch perception by using MRI and magnetoencephalography (MEG) and (iii) the influence of relative hemispheric lateralization versus absolute magnitude of both gray matter volume structurally and auditory evoked activity functionally.

[1]Department of Neurology, University Hospital Heidelberg, INF 400, D-69120 Heidelberg, Germany. [2]School of Health Sciences, Division of Medical Imaging, University of Liverpool, Johnston Building, The Quadrangle Brownlow Hill, Liverpool L69 3GB, UK. [3]Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool, Pembroke Place, PO Box 147, Liverpool, L69 3BX, UK. [4]Department of Cognitive Neuroscience, Faculty of Psychology, Universiteit Maastricht, Postbus 616, 6200MD Maastricht, The Netherlands. [5]Department of Physics, University of Heidelberg, Philosophenweg 12, D-69120 Heidelberg, Germany. [6]Institute of Sound and Vibration Research, University of Southampton, University Road Highfield, Southampton S017 1BJ, UK. Correspondence should be addressed to P.S. (Peter.Schneider@med.uni-heidelberg.de).

Published online 21 August 2005; doi:10.1038/nn1530

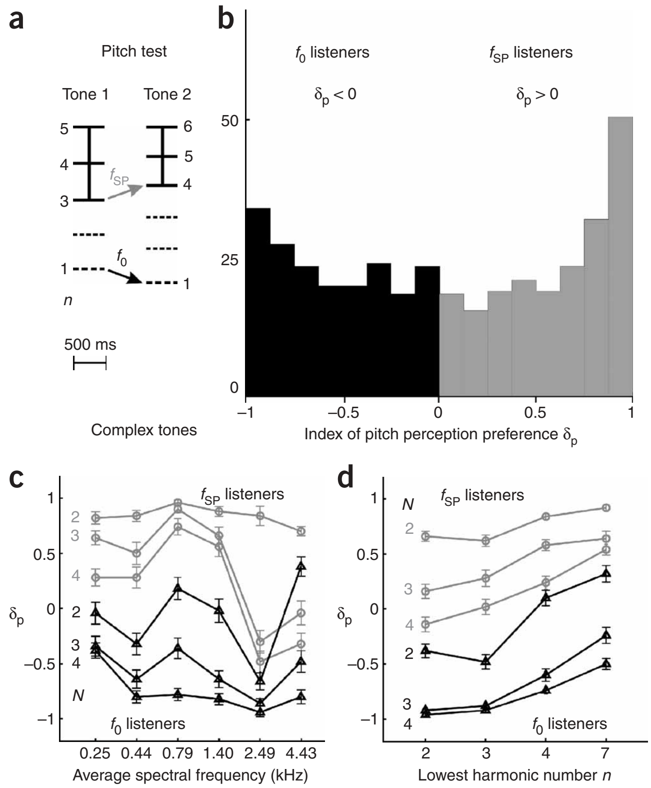

Figure 1 Psychometric testing and grouping. (**a**) Experimental design: participants were required to state the dominant direction of pitch shift between tone pairs. Solid lines represent the harmonics of the test tones and dashed lines the harmonics which are not physically present, such as the missing fundamental, indicated as number 1. (**b**) Bimodal distribution of fundamental (f_0) and spectral pitch (f_{SP}) listeners. (**c**,**d**) Perceptual changes as a function of the acoustic variables. The dependence on frequency (f) and lowest order of harmonics are depicted in separate curves for stimuli composed of $N = 2$, 3 and 4 adjacent harmonics. n indicates the order of harmonics in a complex tone; that is, an integer multiple of the fundamental frequency ($f_{SP} = n \times f_0$). N is the number of physically present harmonics (on the left of each curve).

RESULTS

Psychometric testing and grouping

A psychometric pitch test was designed on the basis of standard methodology[1,2] for a parametric range that was extended with respect to the typical pitch range of musical instruments. The test required participants to state the dominant direction of pitch shift between items in each of a total of 144 pairs of complex tones with systematic variation of frequency (f), order of harmonics (n) (that is, a multiple integer of the fundamental frequency ($f_{SP} = n \times f_0$)) and number (N) of present harmonics. The stimuli were such that the perceived direction of the shift in pitch between the two tones was dependent upon whether they are decoded in f_0 or f_{SP} pitch (**Fig. 1a**). Accordingly, for each individual a psychometric asymmetry coefficient was derived by recording the number of occasions of f_0 listening versus f_{SP} listening and computing an 'index of pitch perception preference' $\delta_p = (f_0 - f_{SP}) / (f_0 + f_{SP})$. Analysis of the psychometric data of a large sample of 373 musicians including symphony orchestra musicians[28] and 48 non-musicians showed that δ_p demonstrated a broad bimodal distribution (**Fig. 1b**), which allowed for a dichotomous classification of all subjects as belonging to one of two behavioral groups, either 'f_0 listeners' ($\delta_p < 0$) or 'f_{SP} listeners' ($\delta_p > 0$). The overall strong separation was most pronounced in the lower (**Fig. 1c**, spectral frequencies <1,500 Hz, $F_{1,419} = 731.4$, $P < 0.0001$) as compared with the higher spectral frequency range. Furthermore, the tendency to base direction of pitch judgments on the implied f_0 increased systematically with increasing number (N) of components (**Fig. 1c**, $F_{2,838} = 498.5$, $P < 0.0001$) and with decreasing order (n) of harmonic number (**Fig. 1d**, $F_{2,838} = 352.8$, $P < 0.0001$). The separation of f_0 and f_{SP} listeners was such that a two-component stimulus ($N = 2$) had even stronger fundamental pitch character for f_0 listeners as a four-component stimulus ($N = 4$) had for f_{SP} listeners.

Neural basis of pitch perception

MRI of brain structure and functional MEG of neural activity in response to harmonic complex tones were performed in a subgroup of 34 f_0 and 53 f_{SP} listeners and demonstrated a strong neural basis for type of pitch perception. The individual surfaces of all 87 left and right auditory cortices were segmented and reconstructed three dimensionally from the T1-weighted MRI slices (**Fig. 2a**). The pronounced oblique crescent-shaped gyral entity in anterior auditory cortex, including HG in its mediolateral extent and aSTG anterolaterally, was always identified by detection of the first complete Heschl's sulcus (cHS) as posterior boundary of HG and the first transverse sulcus (FTS) as the anterior boundary (**Fig. 2b–d**, red). HG may include incomplete duplications by a sulcus intermedius (SI)[29–32] indenting locally its crown or a medial Heschl's sulcus (mHS), not reaching the lateral end. We next calculated the gray matter volume along the medial-lateral-anterior progression of this anterior gyrus (**Fig. 2b**, dashed lines), by marking the corresponding gray values successively in cross-sectional slices perpendicular to the orientation of HG and aSTG. Overall, the gray matter volume increased successively from mHG to aSTG (**Fig. 2e,f**). When comparing the volumes of the left and the right hemispheres, we found a characteristic asymmetry exclusively within the lateral aspect of HG irrespective of musical aptitude. The f_0 listeners demonstrated a pronounced leftward asymmetry (**Fig. 2e**), whereas f_{SP} listeners demonstrated a pronounced rightward asymmetry (**Fig. 2f**). The asymmetry started at the lateral border of mHG, peaked within the lateral edge of HG and was absent in aSTG.

This structural asymmetry was paralleled by a corresponding functional asymmetry. In particular, we performed an MEG study in which subjects were instructed to listen passively to harmonic complex tones covering the large parametric range of the pitch test. Auditory evoked fields were recorded continuously over both hemispheres. The source activity was calculated from the sensor distribution by modeling one equivalent dipole in each hemisphere. When fitted to the secondary P50m response peaking 50 ms after tone onset (P50m), the dipoles localized in the lateral portion of HG in most cases. **Figure 2g,h** shows the group-averaged source waveforms for professionals and non-musicians. P50m magnitude was larger in the left hemisphere for f_0 listeners (professionals: factor 1.3 ± 0.2, $F_{1,33} = 6.2$, $P < 0.01$; non-musicians: factor 1.5 ± 0.2, $F_{1,9} = 14.5$, $P < 0.01$) and in the right hemisphere for f_{SP} listeners (professionals: factor 1.3 ± 0.2, $F_{1,29} = 22.4$, $P < 0.0001$; non-musicians: factor 1.6 ± 0.3, $F_{1,9} = 7.7$, $P < 0.01$). No significant hemispheric asymmetry was observed for the early P30m (ref. 27) and the pitch-sensitive N100m response[10,33].

Morphometry of auditory cortex subregions

Based on this specific connection of structural and functional asymmetry in relation to pitch perception, we identified objective criteria to define lHG. After normalization[34], a grand-average auditory cortex

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

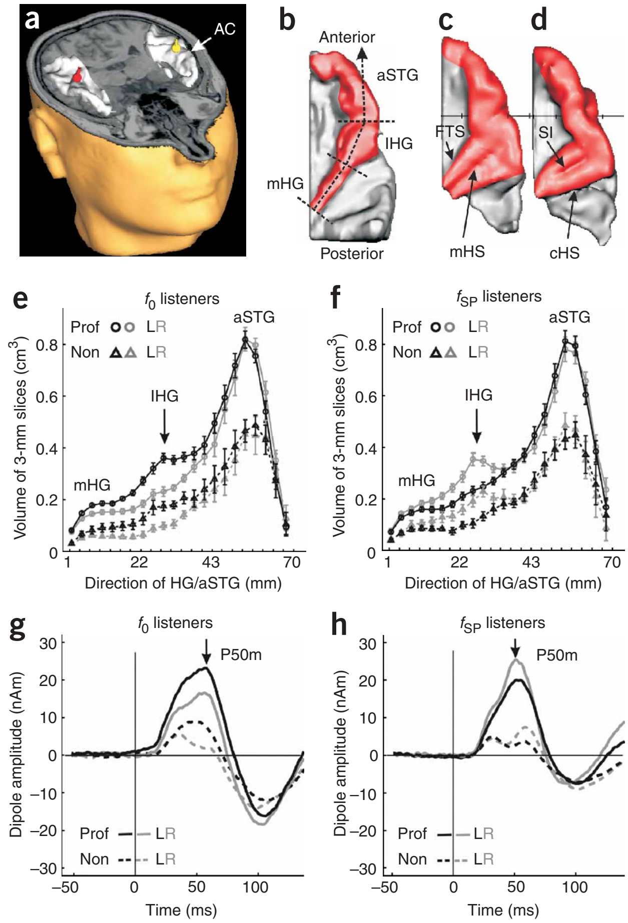

Figure 2 Neural basis of fundamental and spectral pitch perception. (**a**) 3D reconstruction of an individual auditory cortex and auditory evoked activity (blue and red dipoles). (**b**–**d**) The top view of three individual 3D surface reconstructions of right auditory cortex shows the pronounced gyral entity including HG and aSTG (colored red), bordered anteriorly by the first transverse sulcus (FTS) and posteriorly by the first complete Heschl's sulcus (cHS). HG may include a sulcus intermedius (SI), indenting locally the crown of HG, or a medial Heschl's sulcus (mHS), not reaching the lateral end. Gray matter volume was successively calculated in cross-sectional slices along the medial-lateral-anterior progression. (**e**,**f**) Fundamental pitch listeners demonstrated a pronounced leftward asymmetry of gray matter volume and spectral pitch listeners a rightward asymmetry, peaking within the lateral one-third of HG. (**g**,**h**) Functional asymmetry of the auditory evoked P50m source activity of lHG in response to harmonic complex tones. P50m magnitude was relatively larger in the left hemisphere for f_0 listeners and vice versa for f_{SP} listeners, irrespective of musical aptitude. Prof, professional musician; non, non-musician, in all figures.

map of all 87 brains was calculated from the individual landmarks of FTS, cHS and posterior border of planum temporale (PT)[35]. The top view of this map is depicted in **Figure 3**. Despite large individual differences in shape and progression of HG, the grand average over all 87 right and left auditory cortices demonstrated a completely symmetric organization with respect to angulation, extent and transition from HG to aSTG. However, the PT clearly showed the expected leftward asymmetry. Secondly, functional activation peaks in relation to pitch perception[8,15–17,19,20,23,36] were plotted on this averaged auditory cortex map (**Fig. 3**, magnified HG). The main activation peaks concerning pitch perception are all confined to the lateral portion of HG (x-range: ± 45 to ± 65; y-range: –20 to 0). Melody-specific activation[7,13,16,23] originates more anterior ($y > 0$) in aSTG. Our own findings on lateralization (**Fig. 2e,f**), the current knowledge of primary auditory cortex extent[16,29–31,37–40] and the functional separation of adjacent pitch-sensitive areas[14–17] were used as criteria to define objective boundaries of lHG: (i) a line perpendicular to the progression of HG at the mediolateral two-thirds to separate the region of mHG and lHG; (ii) a line at $y = 0$ to separate the region of lHG ($y < 0$, highlighted) and aSTG ($y > 0$, colored in **Fig. 3**). By strict application of these boundary definitions, the gray matter volumes of mHG, lHG, aSTG and PT were calculated. Only lHG demonstrated a strong leftward asymmetry in f_0 listeners and rightward asymmetry in f_{SP} listeners (**Table 1**). The individual auditory cortex morphology of 32 professional musicians, eight amateur musicians and eight non-musicians (**Fig. 4**) illustrates (i) the large individual differences with respect to angulation and progression of HG, (ii) the differences in structural left-right asymmetry of lHG in relation to pitch perception and (iii) the structural enlargement of the entire anterior crescent-shaped gyrus in musicians as compared with non-musicians. The frequency of duplications or sulci depends on hemisphere and on perceptual preference (**Table 2**).

Structural, functional and perceptual asymmetry

Corresponding to the definition of perceptual asymmetry, the structural and functional asymmetry of lHG was measured in terms of a 'structural asymmetry index' $\delta_s = (R_{lHG} - L_{lHG})/(R_{lHG} + L_{lHG})$ and a 'functional P50m asymmetry index' $\delta_f = (R_{P50m} - L_{P50m})/(R_{P50m} + L_{P50m})$. The correlation of δ_s versus δ_p was calculated separately by systematically including or excluding HG duplications: (i) all duplications including complete posterior duplications (PDs) were included

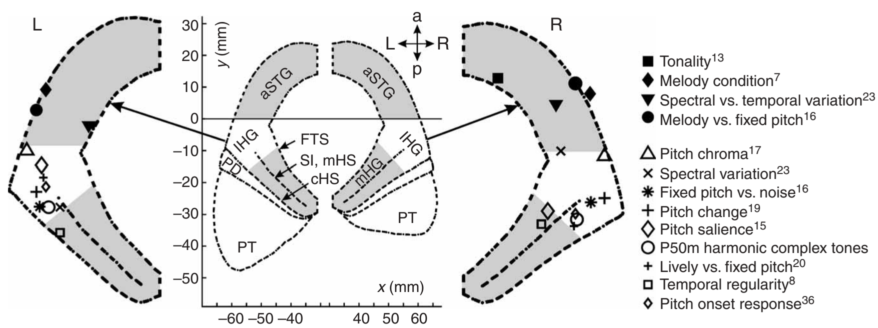

Figure 3 Averaged landmarks of 87 auditory cortices (top view, standard stereotaxic coordinates[34]; line width of the dashed landmarks corresponds to averaged s.e.m.). The crescent-shaped anterior gyrus including HG and anterior supratemporal gyrus (aSTG) showed a completely symmetric shape and progression with respect to angulation, extent, duplications and curvature. A complete posterior duplication (PD) was considered to be part of the planum temporale (PT). The main activation peaks of functional imaging studies are plotted on the magnified map. Black open circles indicate the averaged localization of the auditory evoked P50m response in lHG measured by MEG. Pitch-specific activation localized in lHG, melody-specific activation more anterior in aSTG. In key at right, superscript numbers refer to references.

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

Table 1 Gray matter volume of auditory cortex subregions

	f_0 prof (21)	f_{SP} prof (30)	f_0 non (10)	f_{SP} non (10)	Prof vs. non
Left hemisphere					
mHG_L	1.42 ± 0.07	1.26 ± 0.06	0.70 ± 0.05	0.73 ± 0.06	***
lHG_L (highlighted)	2.09 ± 0.14***	1.67 ± 0.09	1.20 ± 0.06**	0.87 ± 0.11	***
$aSTG_L$	5.14 ± 0.32	5.02 ± 0.21	3.48 ± 0.26	3.47 ± 0.23	***
PT_L	4.03 ± 0.32*	4.38 ± 0.28**	3.63 ± 0.41	3.59 ± 0.34*	n.s.
Right hemisphere					
mHG_R	1.25 ± 0.07	1.37 ± 0.06	0.61 ± 0.11	0.79 ± 0.07	***
$lHG_{\mathbf{R}}$ (highlighted)	1.61 ± 0.12	2.21 ± 0.12**	0.73 ± 0.10	1.22 ± 0.09**	***
$aSTG_R$	5.09 ± 0.42	4.55 ± 0.20	3.49 ± 0.26	3.05 ± 0.14	***
PT_R	3.23 ± 0.31	2.65 ± 0.16	3.26 ± 0.29	2.58 ± 0.25	n.s.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ ANOVA, left versus right hemisphere (designating the dominant hemisphere), Prof vs. non, overall significance of professionals versus non-musicians). mHG, medial Heschl's gyrus; lHG, lateral Heschl's gyrus; aSTG, anterior supratemporal gyrus; PT, planum temporale. Values: mean (cm^3) ± s.e.m., standard stereotactic voxel size[29]. Prof, professional musician. Non, non-musician; n.s., not significant.

($r = 0.47$, $P < 0.0001$); (ii) right and left PD's were excluded; that is, cHS was always the posterior boundary ($r = 0.77$, $P < 0.0001$); (iii) only left PDs were excluded, ($r = 0.81$, $P < 0.0001$); (iv) all duplications posterior to cHS and mHS were excluded ($r = 0.70$, $P < 0.0001$); or (v) all duplications posterior to cHS, mHS and SI were excluded; that is, the anterior HG[27] was considered ($r = 0.38$, $P < 0.001$). Overall, the correlation remained strongly robust irrespective of inclusion or exclusion of duplications. However, with respect to a symmetric definition of boundaries, the effect was most pronounced if cHS was always the posterior boundary (case 2, **Fig. 5a**). The scatter plot of P50m asymmetry (δ_f) versus pitch perception asymmetry (δ_p) demonstrated again a robust effect ($r = 0.63$, $P < 0.0001$, **Fig. 5b**). As a consequence, structural and functional asymmetry of lHG was strongly linked ($r = 0.55$, $P < 0.001$). However, if absolute magnitude of the neural substrate was considered instead of the relative hemispheric asymmetries, the correlation dropped to insignificance (P50m dipole amplitude versus gray matter volume of lHG: $r = 0.04$, n.s.).

Influence of musical ability

With respect to the absolute magnitude of the neural lHG substrate, large group-specific differences were found, corroborating and extending earlier findings[27]. The crescent-shaped anterior convolution of auditory cortex including mHG, lHG and aSTG, colored in red (right hemisphere) and in blue (left hemisphere, **Figs. 2b–d** and **4**), demonstrated strongly enlarged gray matter volume in professional musicians as compared with non-musicians (**Table 1**). The gray matter volume correlated significantly with musical aptitude as measured by the Advanced Measure of Music Audiation (AMMA) test[27,41] (lHG: $r = 0.71$, $P < 0.0001$). Furthermore, the auditory evoked P50m response showed a fivefold larger magnitude in professionals as compared with non-musicians (**Fig. 2e,f**; professional: 25.1 ± 1.9 nAm, non-musician: 5.3 ± 1.2 nAm, factor 4.7 ± 0.8, $F_{1,85} = 51.2$, $P < 0.0001$) and correlated with the intensity of musical practice during the last ten years ($r = 0.80$, $P < 0.0001$). No significant correlation was found between any musical ability parameters and neural (δ_f, δ_s) or perceptual (δ_p) asymmetries. As a consequence, the correlations shown in **Figure 5a,b** remained strong for the non-musicians (δ_s versus δ_p: $r = 0.75$, $P < 0.0001$; δ_f versus δ_p: $r = 0.67$, $P < 0.0001$).

DISCUSSION

Application of an auditory judgment task that is known to produce large perceptual differences across individuals[1,2] in the investigation of a large sample of musicians and non-musicians enabled a systematic categorization in f_0 and f_{SP} listeners. The f_0 listeners tended to base direction of pitch change judgments on the implied fundamental frequency, whereas the f_{SP} listeners performed the pitch change

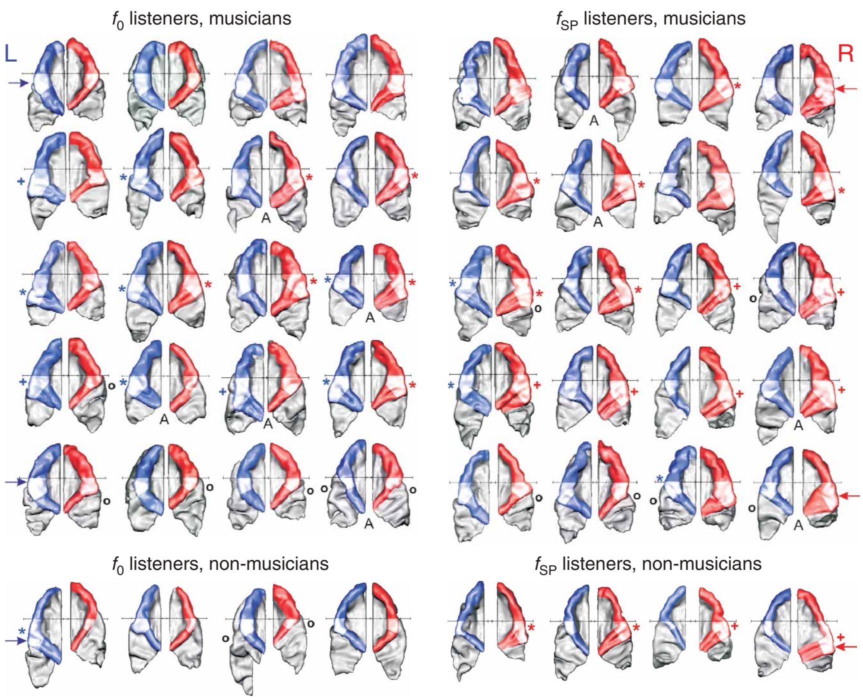

Figure 4 Individual HG morphology. f_0 listeners demonstrate a larger left lHG and f_{SP} listeners a larger right lHG in most cases (lHG highlighted, red and blue arrows). The occurrence of sulci and duplications (SI, asterisks; mHS, '+' symbols; PD, black open circles) depends on hemisphere and pitch perception preference. Professional musicians and amateurs (A) showed greater gray matter volume of the entire anterior convolution including HG and aSTG (colored structure) than non-musicians (bottom).

Table 2 Frequency of HG duplications and sulci

	SI	mHS	PD	Single HG
f_0 listener (33)				
Only right HG	6	1	3	5
Only left HG	4	2	6	6
Left and right HG	3	0	2	19
Without	20	30	22	3
f_{SP} listener (54)				
Only right HG	29	9	6	0
Only left HG	0	1	10	36
Left and right HG	6	1	1	11
Without	19	43	37	9

SI, sulcus intermedius; mHS medial Heschl's sulcus; PD, complete posterior duplication. The frequency of HG duplications or sulci (given by the number of observed cases from all 87 subjects) depends on hemisphere and on perceptual preference. In particular, for all 39 cases where either in the left or in the right hemisphere a SI was present, the frequency differed significantly for f_{SP} listeners as compared to f_0 listeners ($\chi^2(1) = 12.9$, $P < 0.001$).

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

judgment on the basis of the spectral envelope rather than fundamental frequency. By using MRI and MEG we found a strong neural basis of both types of pitch perception, which corroborated the functional specialization of left auditory cortex for rapid temporal[23,25] and the right hemisphere for spectral[23] processing.

The pitch test allowed systematic analysis of the influence of acoustic stimulus properties on pitch perception. First, the separation of f_0 and f_{SP} listeners was much stronger within a spectral frequency range below 1,500 Hz and decreased towards the higher frequencies. This may be reflected in the psychometric 'dominance principle'[42], stating that the center of harmonic order which is dominant for pitch perception decreases from $n = 5$ ($f_0 = 200$ Hz) to $n = 1$ ($f_0 = 2{,}000$ Hz). Second, the general increase of f_0 dominance with decreasing n and increasing N (**Fig. 1c,d**) corroborates the current knowledge of fundamental pitch saliency[2,10,42]. However, our data emphasize that pitch perception depends on both spectral envelope and fundamental frequency information with different weighting and cannot be explained by a simple one-to-one relationship between perceived pitch and fundamental frequency[6,10]. A functional separation of periodicity coding and spectral integration at the level of auditory cortex may account for the different pitch percepts, varying between individuals by up to three or four octaves, when the same sound was presented.

The large perceptual dissimilarity in pitch perception was paralleled by a strong inter-individual structural and functional variability in auditory cortex. To visualize this pronounced variation, which was anticipated a long time ago from myelogenetic studies[40], we depicted for the first time the full shape and progression of HG and aSTG, forming together a crescent-shaped gyral entity of the anterolateral stream in human auditory cortex[14]. The huge morphological differences with respect to angulation, extent of HG and its oblique transition towards aSTG were superposed by a conspicuous increase of gray matter volume in musicans[27,43] (**Fig. 4**). Averaged over 87 subjects, the shape was completely symmetric, whereas some morphometric studies show asymmetric average maps[29,32]. However, these and our studies are not sufficiently comparable owing to differences in sample size, definition of boundaries and extent of the region of interest. Furthermore, detailed morphometric analysis showed that the correlation between preference of f_0 versus f_{SP} perception and neural asymmetry was confined to lHG and was not present for the entire body of HG or aSTG. In particular, f_0 listeners demonstrated an asymmetry favoring the left lHG in terms of both cortical gray matter volume and auditory evoked P50m activity, whereas f_{SP} listeners showed the opposite asymmetry. This corroborated the functional specialization of lHG as a pitch processing center[12]. Our results imply a left-hemispheric specialization for (missing) fundamental pitch perception and a right hemispheric specialization for spectral pitch perception, consistent with a recent functional imaging study comparing the neural processing of spectral and temporal variation[23]. Furthermore, left auditory cortex is sensitive to short time scales (25–50 ms)[25,44] and right auditory cortex to slower time scales (200–300 ms)[25]. The fundamental pitch (f_0) of an instrumental sound ($f_0 > 25$ Hz) reflects its periodicity[6] $T = 1/f_0$, corresponding to time segments shorter than 40 ms. Thus, the existence of two pitch centers may facilitate the extraction of fundamental pitch in left auditory cortex and spectral pitch in right auditory cortex. Indeed, most professional musicians perceive simultaneously both fundamental and spectral pitch from an ambiguous tone, and the subjective differences are rather relative than absolute[24]. Here, these relative perceptual differences were found to correlate strongly to neural asymmetries, as anticipated by earlier studies on cerebral dominance[45]. Thus, a greater volume on the left may predispose one to hear the f_0 in an ambiguous tone, and vice versa, a greater volume on the right may lead to a dominant perception of spectral pitch or single harmonics. A psychophysical study on patients with temporal lobe lesions demonstrates fourfold higher thresholds for determining the direction of pitch changes in patients with right hemisphere lesions that encroached on HG. This study concludes that detecting the direction of pitch changes may depend largely on the right HG[18]. However, there is no conflict with our results, because the magnitudes of pitch changes used in our study were largely above the f_0 discrimination thresholds investigated in the lesion study. Thus, the latter may reflect in particular the accuracy of pitch direction judgment relative to the magnitude of f_0 discrimination, irrespective of general left-right hemispheric lateralization effects in pitch perception.

The direct link between structural and functional asymmetries reported here seems to be confined to a local mechanism within the pitch center of lateral HG, present only in a small time range of 30–40 ms around P50m activity of the MEG recordings. The main activation peaks from comparable fMRI[15,16] studies depict the activity within a much larger time frame of several seconds, including other activities which originate partially from lateral HG, in particular the pitch-sensitive N100 activity[10,33] and the pitch onset response[36] occurring about 130 ms after tone onset. Overall, functional asymmetries are not always observed in every task, subject, stimulus condition or specified

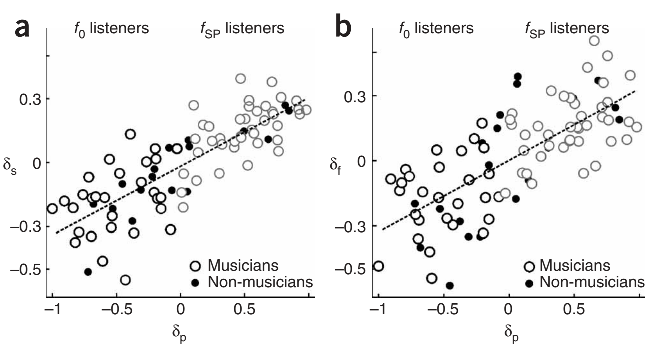

Figure 5 Pitch perception preference and neural asymmetries. (**a**) Correlation of pitch asymmetry (δ_p) versus structural asymmetry (δ_s) of gray matter in lHG. (**b**) Correlation of pitch asymmetry (δ_p) versus functional asymmetry (δ_f) of P50m magnitude. The correlations are strong irrespective of musical aptitude.

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

processing level. In some cases or individuals the activation maps really are symmetric[14,16,20]. However, with respect to pitch- or melody-related tasks, the majority of functional imaging studies[14,16,23,24] showed right-sided asymmetries. Multimodal functional imaging with professional musicians may help to clarify under which conditions the observed pitch asymmetries arise.

Our findings demonstrate a strong correlation between the relative hemispheric lateralization of structure and function and perceptual preference, as confirmed by morphometric[31,45,46] and functional imaging studies[25]. In contrast, absolute magnitudes of the neural HG substrate depend on musical expertise consistent with previous studies[27,33,47,48]. At a more fundamental level, a recent post-mortem study observed characteristic asymmetries in auditory belt areas at the level of the underlying microanatomical architecture[26]. However, the exact relation between absolute changes at the microanatomical and macroanatomical level still remains unclear and needs further clarification. Use-dependent subcortical changes such as dendritic arborization changes or interdigitation of neuronal clusters[26] may enhance the magnitude of synchronized postsynaptic potentials as measured by MEG in professional musicians without changing, however, the cortical thickness or volume of the underlying gray matter tissue. Likewise, a larger HG gray matter volume implies a larger neural network *per se*, independent of neural connectivity, and may reflect a greater potential of musical aptitude. A strong relation between absolute magnitudes of structure and function was observed at the early automatic processing level in anteromedial HG[27] and obviously disappears in secondary auditory cortex. Post-mortem studies[29,30] showed considerable variation between structure and function when comparing the boundaries of individual microanatomical structure and macroanatomical visible magnetic resonance landmarks. These results suggest that the functional areas do not correspond to areas defined on the basis of macroscopic boundaries. Nevertheless, when calculating micro- and macroanatomical probability maps, the corresponding centroids of the location were found to be almost identical[14,16,29]. As a consequence, despite large individual variability[29], the medial two-thirds of anterior HG were considered a reliably good approximation of the anterolateral extent of primary auditory cortex[16,24,37], as confirmed by cytoarchitectonic[38], histochemical[39] and myelogenetic[40] studies. Overall, we conclude that the relative hemispheric lateralization of functional and structural size reflects the type of pitch processing irrespective of musical aptitude, whereas the absolute magnitudes of the neural HG substrate depends on musical expertise. Further studies may clarify whether the observed lateralization is linked to a preference for characteristic physical sound properties (in particular, the faster temporal structure of percussive sounds versus the slower time scale of sustained sounds[25,49,50]) therefore influencing musical instrument preference and musical performance.

METHODS

Subjects. A large sample of 420 right handed healthy subjects (125 professional musicians including members of the Royal Liverpool Philharmonic Orchestra[28], 181 graduate students in music, 66 amateur musicians and 48 non-musicians) were recruited for the psychometric evaluation of pitch perception and evaluation of musical aptitude. A subgroup of 87 subjects participated in the MRI and MEG measurements (out of 51 professionals, including 21 members of the Royal Liverpool Philharmonic Orchestra, 16 amateurs and 20 non-musicians, 34 were f_0 and 53 f_{SP} listeners). Averaged over the groups, no significant differences in age, sex and head size were observed. Experimental procedures were approved by the relevant local research ethics committee.

Pitch test. The pitch test included 144 different pairs of harmonic complex tones. Each tone pair consisted of two consecutive harmonic complex tones (duration 500 ms, 10-ms rise-fall time, interstimulus interval 250 ms). Each test tone comprised two, three or four adjacent harmonics, leaving out the fundamental frequency. Overall, the tone pairs were designed with six different upper component frequencies (293, 523, 932, 1,661, 2,960 and 5,274 Hz) chosen to be equidistant on a logarithmical frequency scale corresponding to the musical interval of a major ninth, beginning with D3 (293 Hz) up to C8 (5,274 Hz). The upper component frequency of both tones in each tone pair was identical to minimize the perception of edge pitch. Furthermore, the lowest presented harmonic number transitions ($n_{1,\min} \rightarrow n_{2,\min}$) within a tone pair was one of the following four conditions: $2 \rightarrow 3$, $3 \rightarrow 4$, $4 \rightarrow 6$ or $7 \rightarrow 9$. Thus, the spectral components ranged between 146 and 5,274 Hz and f_0 between 29 to 1,318 Hz. The magnitude of f_0 pitch changes ranged between a factor of 1.1 (major second) to 1.8 (minor seventh); the f_{SP} pitch changes of the lowest harmonic number ranged from a factor of 1.1 to 3.1. Thus, the magnitude of these pitch changes was considerably larger than pitch discrimination threshold[18]. By using additionally complete harmonic complex tones ($n_{\min} = 1$) as reference tones (conditions $2 \rightarrow 1$, $3 \rightarrow 1$, $4 \rightarrow 1$ and $5 \rightarrow 1$), the pitch test allowed detection of octave-shifted fundamental pitches (for instance, one octave above f_0). This case occurred only significantly for three-component stimuli within the higher spectral range ($>$1,000 Hz) and was not considered to be part of f_0 perception. However, if fundamental pitch perception would mean both f_0 and octave-shifted f_0 perception, our results would not qualitatively change. All stimuli were presented binaurally in pseudorandomized order using a Hammerfall DSP Multiface System with a stimulus level of 50 dB nSL to avoid the interfering superposition of combination tones. Each tone pair was repeated once and the next new tone pair presented after a pause of 2 s. Subjects were instructed to select the dominant pitch direction or to answer according to the first, spontaneous impression, if either both directions were perceived at the same time or if tones lacked a clear pitch. Test duration was 22 min. All subjects were tested on an identical set of stimuli. A subgroup of 37 subjects repeated the pitch test about 6 months later and demonstrated strong individual re-test reliability ($r = 0.96$, $P < 0.0001$).

Morphometry. The three-dimensional (3D) gray matter surface reconstructions of all individual auditory cortices were calculated from T1-weighted structural MRI data (Siemens, Symphony, 1.5-T) after segmentation using BrainVoyager software (Brain Innovation). All brains were rotated in direction of the antero-posterior commissural line and normalized by unfiltered transformation in Talairach space[34]. Using standard definitions of the anatomical auditory cortex landmarks[29–32,35,37], the sagittal MRI slices of the individual auditory cortices were segmented along the Sylvian fissure to obtain PT, HG and aSTG. The inclusion range of image gray values was calculated in a normalized box around left and right auditory cortex. For gray matter surface reconstruction and morphometry, the 'gray value inclusion range' was defined individually from the intensity histogram of gray values for each left and right auditory cortex, by identifying (i) the half-amplitude side-lobe of the gray matter peak distribution towards cerebral spinal fluid and (ii) the saddle point between the gray and white matter peak. All gray value voxels inside this inclusion range were marked and used for 3D reconstruction and morphometry. The non-automated parts of this structural analysis (in particular, the identification of individual landmarks from the individual 3D surface reconstructions of auditory cortex) were obtained by observers who were blind to subject group and hemisphere.

HG subregions. Here we used the most obvious and well-accepted definition of HG[29,30] by identifying the first complete Heschl's sulcus (cHS) as its posterior and the crescent-shaped first transverse sulcus (FTS)[29–32] as its anterior boundary. cHS was identified by virtue of having a clear lateral indentation (**Fig. 2d**), large mediolateral extent and pronounced depth, and divided auditory cortex in two parts: (i) an anterior auditory stream including HG and aSTG and (ii) a posterior stream including the PT. Based on normalization, the pronounced crescent-shaped gyrus anterior to cHS was subdivided systematically in mHG, lHG and aSTG. By using functional and structural criteria (**Fig. 3**), the $y = 0$ line was found to be an appropriate borderline to separate HG and aSTG. Individual extrapolation of FTS towards the lateral end of HG, as proposed by some morphometric studies[31,32,37], was impossible in our sample owing to large individual differences with respect to angulation and asymmetric progression (**Fig. 4**). The extent of mHG was defined by the medial two-thirds of HG along the mediolateral direction of HG, similar to the estimated extent of primary auditory cortex[16,29,30]. lHG was the remaining part of the gyrus between aSTG and mHG. The gray matter volume of each specified subregion was calculated by marking and counting all included gray values of the individual gray matter peak distribution (see above). Finally, the volume of lHG was the difference between the volumes of HG and mHG.

Magnetoencephalography. Using a Neuromag-122 whole-head MEG system, we recorded auditory evoked fields to twelve harmonic complex sounds covering the parametric range as used for the pitch test (f_0: 100 and 500 Hz, lowest number of harmonics: 1, 4 and 10, complete spectrum and three adjacent harmonics). Subjects were instructed to listen passively to the sounds, each of which was presented 240 times in pseudorandomized order. Cortical responses were averaged for each frequency using the BESA program (MEGIS Software) and collapsed into an individual grand average for source analysis (3,600 averages). The source activity of the auditory evoked P50m response was separated from the earlier P30m and later N100m response by spatiotemporal source modeling[27], using one equivalent dipole in each hemisphere. The fitting intervals were adjusted to the individual source waveforms in time intervals around the peaks defined by their half–side lobes. Signal strength was calculated for each peak relative to a 100 ms baseline.

© 2005 Nature Publishing Group http://www.nature.com/natureneuroscience

ACKNOWLEDGMENTS
We thank K. Sartor for providing the 3D-MRI in Heidelberg, the radiographic staff at MARIARC for assistance with MRI data acquisition in Liverpool and E. Hofmann (Music Academy, Basel); D. Geller, R. Schmitt and T. van der Geld (University of Music and Performing Arts, Mannheim); C. Klein (Institute of Music Pedagogy, Halle) and D. Schmidt (Conservatory of Music and Performing Arts, Stuttgart) for assistance with collecting the psychometric data.

COMPETING INTERESTS STATEMENT
The authors declare that they have no competing financial interests.

Received 15 April; accepted 28 July 2005
Published online at http://www.nature.com/natureneuroscience/

1. Smoorenburg, G.F. Pitch perception of two-frequency stimuli. *J. Acoust. Soc. Am.* **48**, 924–942 (1970).
2. Laguitton, V., Demany, L., Semal, C. & Liégeois-Chauvel, C. Pitch perception: a difference between right-and left-handed listeners. *Neuropsychologia* **36**, 201–207 (1998).
3. von Helmholtz, H.L.F. *On the Sensations of Tone* (Longmans, London, 1885).
4. Terhardt, E. Pitch, consonance and harmony. *J. Acoust. Soc. Am.* **55**, 1061–1069 (1974).
5. Wessinger, C.M. *et al.* Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging. *J. Cogn. Neurosci.* **13**, 1–7 (2001).
6. Langner, G. Periodicity coding in the auditory system. *Hear. Res.* **60**, 115–142 (1992).
7. Griffiths, T.D., Büchel, C., Frackowiak, R.S.J. & Patterson, R.D. Analysis of temporal structure in sound by the human brain. *Nat. Neurosci.* **1**, 422–427 (1998).
8. Gutschalk, A., Patterson, R.D., Rupp, A., Uppenkamp, S. & Scherg, M. Sustained magnetic fields reveal separate sites for sound level and temporal regularity in human auditory cortex. *Neuroimage* **15**, 207–216 (2002).
9. Formisano, E. *et al.* Mirror-symmetric tonotopic maps in human primary auditory cortex. *Neuron* **40**, 859–869 (2003).
10. Pantev, C., Hoke, M., Lütkenhöner, B. & Lehnerz, K. Tonotopic organization of the auditory cortex: pitch versus frequency representation. *Science* **246**, 486–488 (1989).
11. Seifritz, E. *et al.* Spatiotemporal pattern of neural processing in the human auditory cortex. *Science* **297**, 1706–1708 (2002).
12. Griffiths, T.D. Functional imaging of pitch analysis. *Ann. NY Acad. Sci.* **999**, 40–49 (2003).
13. Janata, P. *et al.* The cortical topography of tonal structures underlying western music. *Science* **298**, 2167–2170 (2002).
14. Hall, D. *et al.* Spectral and temporal processing in human auditory cortex. *Cereb. Cortex* **12**, 140–149 (2002).
15. Penagos, H., Melcher, J.R. & Oxenham, A.J. A neural representation of pitch salience in nonprimary human auditory cortex revealed with functional magnetic resonance imaging. *J. Neurosci.* **24**, 6810–6815 (2004).
16. Patterson, R.D., Uppenkamp, S., Johnsrude, I.S. & Griffiths, T.D. The processing of temporal pitch and melody information in auditory cortex. *Neuron* **36**, 767–776 (2002).
17. Warren, J.D., Uppenkamp, S., Patterson, R. & Griffiths, T.D. Separating pitch chroma and pitch height in the human brain. *Proc. Natl. Acad. Sci. USA* **100**, 10038–10042 (2003).
18. Johnsrude, I.S., Penhune, V.B. & Zatorre, R.J. Functional specificity in the right human auditory cortex for perceiving pitch direction. *Brain* **123**, 155–163 (2000).
19. Warren, J.D. & Griffiths, T.D. Distinct mechanisms for processing spatial sequences and pitch sequences in the human auditory brain. *J. Neurosci.* **23**, 5799–5804 (2003).
20. Griffiths, T.D., Uppenkamp, S., Johnsrude, I., Josephs, O. & Patterson, R.D. Encoding of the temporal regularity of sound in the human brainstem. *Nat. Neurosci.* **4**, 633–637 (2001).
21. Tervaniemi, M. Lateralization of auditory-cortex functions. *Brain Res. Brain Res. Rev.* **43**, 231–246 (2003).
22. Devlin, J.T. *et al.* Functional asymmetry for auditory processing in human primary auditory cortex. *J. Neurosci.* **23**, 11516–11522 (2003).
23. Zatorre, R. & Belin, P. Spectral and temporal processing in human auditory cortex. *Cereb. Cortex* **11**, 946–953 (2001).
24. Zatorre, R.J., Belin, P. & Penhune, V. Structure and function of auditory cortex: music and speech. *Trends Cogn. Sci.* **6**, 37–46 (2002).
25. Boemio, A., Fromm, S. & Poeppel, D. Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nat. Neurosci.* **8**, 389–395 (2005).
26. Galuske, R.A., Schlote, W., Bratzke, H. & Singer, W. Interhemispheric asymmetries of the modular structure in human temporal cortex. *Science* **289**, 1946–1949 (2000).
27. Schneider, P. *et al.* Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nat. Neurosci.* **5**, 688–694 (2002).
28. Sluming, V. *et al.* Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians. *Neuroimage* **17**, 1613–1622 (2002).
29. Rademacher, J. *et al.* Probabilistic mapping and volume measurement of human primary auditory cortex. *Neuroimage* **13**, 669–683 (2001).
30. Morosan, P. *et al.* Human primary auditory cortex: cytoachitectonic subdivisions and mapping into a spatial reference system. *Neuroimage* **13**, 684–701 (2001).
31. Penhune, V.B., Zatorre, R.J., MacDonald, J.D. & Evans, A.C. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. *Cereb. Cortex* **6**, 661–672 (1996).
32. Leonard, C.M., Puranik, C., Kuldau, J.M. & Lombardino, L.J. 1998. Normal variation in the frequency and location of human auditory cortex. Heschl's gyrus: where is it? *Cereb. Cortex* **8**, 397–406 (1998).
33. Pantev, C. *et al.* Increased auditory cortical representation in musicians. *Nature* **392**, 811–813 (1998).
34. Talairach, J. & Tournoux, P. *Co-planar Stereotaxic Atlas of the Human Brain* (Thieme, New York, 1988).
35. Westbury, C.F., Zatorre, R.J. & Evans, A.C. Quantifying variability in the planum temporale: a probability map. *Cereb. Cortex* **9**, 392–405 (1999).
36. Ritter, S., Dosch, H.G., Specht, H.J. & Rupp, A. Neuromagnetic responses reflect the temporal pitch change of regular interval sounds. *Neuroimage* (in the press).
37. Penhune, V.B., Cismaru, R., Dorsaint-Pierre, R., Petitto, L. & Zatorre, R. The morphometry of auditory cortex in the congenitally deaf measured using MRI. *Neuroimage* **20**, 1215–1225 (2003).
38. Galaburda, A. & Sanides, F. Cytoarchitectonic organization of the human auditory cortex. *J. Comp. Neurol.* **190**, 597–610 (1980).
39. Wallace, M.N., Johnston, P.W. & Palmer, A.R. Histochemical identification of cortical areas in the auditory region of the human brain. *Exp. Brain Res.* **143**, 499–508 (2002).
40. Pfeifer, R.A. Pathologie der Hörstrahlung und der corticalen Hörsphäre. in *Handbuch der Neurologie* Vol. 6 (eds. Bumke, O. & Förster, O.) 533–626 (Springer, Berlin, 1936).
41. Gordon, E.E. *Introduction to Research and the Psychology of Music* (GIA, Chicago, 1998).
42. Plomp, R. *Aspects of Tone Sensation* (Academic, London, 1976).
43. Meyer, A. The search for a morphological substrate in the brains of eminent persons including musicians: a historical review. in *Music and the Brain* (eds. Critchley, M. & Henson, R.A.) 255–281. (Heinemann, London, 1977).
44. Rupp, A., Gutschalk, A., Uppenkamp, S. & Scherg, M. Middle latency auditory-evoked fields reflect psychoacoustic gap detection thresholds in human listeners. *J. Neurophysiol.* **92**, 2239–2247 (2004).
45. Galaburda, A.M., Le May, M. & Kemper, T.L. Right-left asymmetries in the brain. Structural differences between the hemispheres may underlie cerebral dominance. *Science* **199**, 852–856 (1978).
46. Schlaug, G., Jäncke, L., Huang, Y. & Steinmetz, H. *In vivo* evidence of structural brain asymmetry in musicians. *Science* **267**, 699–701 (1995).
47. Münte, T.F., Kohlmetz, C., Nager, W. & Altenmüller, E. Superior auditory spatial tuning in conductors. *Nature* **409**, 580 (2001).
48. Gaser, C. & Schlaug, G. Brain structures differ between musicians and non-musicians. *J. Neurosci.* **23**, 9240–9245 (2003).
49. Joliveau, E., Smith, J. & Wolfe, J. Tuning of vocal tract resonance by sopranos. *Nature* **427**, 116 (2004).
50. Belin, P., Zatorre, R.J. & Lafaille, P. Voice-selective areas in human auditory cortex. *Nature* **403**, 309–312 (2000).