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The morphometry of auditory cortex in the congenitally deaf measured using MRI

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Abstract

The study of congenitally deaf individuals provides a unique opportunity to understand the organization and potential for reorganization of human auditory cortex. We used magnetic resonance imaging (MRI) to examine the structural organization of two auditory cortical regions, Heschl's gyrus (HG) and the planum temporale (PT), in deaf and hearing subjects. The results show preservation of cortical volume in HG and PT of deaf subjects deprived of auditory input since birth. Measurements of grey and white matter, as well as the location and extent of these regions in the deaf showed complete overlap both with matched controls and with previous samples of hearing subjects. The results of the manual volume measures were supported by findings from voxel-based morphometry analyses that showed increased grey-matter density in the left motor hand area of the deaf, but no differences between the groups in any auditory cortical region. This increased cortical density in motor cortex may be related to more active use of the dominant hand in signed languages. Most importantly, expected interhemispheric asymmetries in HG and PT thought to be related to auditory language processing were preserved in these deaf subjects. These findings suggest a strong genetic component in the development and maintenance of auditory cortical asymmetries that does not depend on auditory language experience. Preservation of cortical volume in the deaf suggests plasticity in the input and output of auditory cortex that could include language-specific or more general-purpose information from other sensory modalities.
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Introduction

The study of congenitally deaf individuals provides a unique opportunity to understand the organization and potential for reorganization of human auditory cortex. Studies in congenitally deaf individuals stimulated with cochlear implants indicate preserved potential for auditory cortical function (Hari et al., 1988; Okazawa et al., 1996), but suggest that this potential diminishes with age and with duration of deafness (Ponton et al., 1999). Neuroimaging studies show auditory cortical activity in deaf subjects processing sign language and other complex visual stimuli (Finney et al., 2001; Newman et al., 2002; Petitto et al., 2000). But, despite intense current interest in neural plasticity and in the development of cochlear implants, there have been no experiments examining the possible structural changes in human auditory cortex that might underlie the observed functional changes. A single postmortem study of seven individuals with adult-onset deafness showed changes in auditory brainstem nuclei, but did not examine the cortex (Moore et al., 1997). Here, we used volumetric MRI to examine the region of primary auditory cortex, Heschl's gyrus (HG), and a secondary cortical region, the planum temporale (PT), in congenitally deaf individuals. Possible changes in these and other anatomical regions were also assessed using a whole-brain voxel-based technique.

The first question we asked is what global changes might

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occur in auditory cortex as a result of long-term sensory deprivation? Anatomical and physiological studies have shown reduction in the number and activity of neurons and changes in their response properties in the auditory brainstem of congenitally deaf, or experimentally deafened animals (for review, see Shepherd et al., 1997), but studies of auditory cortex have been inconclusive, because of the use of unilaterally deafened animals (McMullen and Glaser, 1988; Reale et al., 1987). More recent studies in congenitally deaf cats have demonstrated microstructural changes in the dendrites in primary auditory cortex (Wurth et al., 1999), as well as changes in electrophysiological function (Klinke et al., 1999; Kral et al., 2000). Finally, human neuroimaging studies with cochlear implant users show variable responsiveness in auditory cortex (Hirano et al., 2000; Naito et al., 1997; Okazawa et al., 1996). However, none of these studies have examined possible structural changes in auditory cortex that might underlie these functional changes.

The second question we asked is whether there might be specific changes in auditory cortex of the congenitally deaf related to auditory language function. Human auditory cortex is characterized by interhemispheric asymmetries in gross morphology and cytoarchitectonic organization. Gross anatomical asymmetries between the hemispheres have been noted since the beginning of the century in both HG (Heschl, 1878; von Economo and Horn, 1930) and PT (Geschwind and Levitsky, 1968; Pfeifer, 1936; von Economo and Horn, 1930). Previous work in our laboratory using structural MRI has documented a L > R asymmetry in the volume of HG (Penhune et al., 1996), and has replicated earlier findings (Galaburda et al., 1978a; Loftus et al., 1993) of an asymmetry in the angulation of the PT (Westbury et al., 1999). The findings of gross anatomical asymmetries have been complemented by cytoarchitectonic studies (Anderson et al., 1999; Galaburda et al., 1978b; Galuske et al., 2000; Morosan et al., 2001; Seldon 1982) showing left-right differences in cellular organization of these regions. These asymmetries have been hypothesized to be related to auditory language processing (Foundas et al., 1994; Galaburda et al., 1978a,b; Geschwind and Levitsky, 1968; Zatorre et al., 2002), but whether they are genetically determined or develop with exposure to auditory language has not been established. This question can be elucidated by determining whether these asymmetries are present in congenitally deaf individuals with no auditory language experience.

Finally, this experiment is also relevant to the question of plasticity or reorganization in auditory cortex. Animal experiments where retinal output is surgically redirected to auditory cortex have shown that auditory cortex can be reorganized to resemble visual cortex in its response patterns and topography (Gao and Pallas, 1999; Sharma et al., 2000), and that these animals can perform visual tasks (Frost et al., 2000; von Melchner et al., 2000). Recent neuroimaging studies in the deaf have found activity in the auditory cortex during processing of sign language and other visual stimuli (Finney et al., 2001; Newman et al., 2002; Petitto et al., 2000), indicative of cortical reorganization. Understanding the structural changes that occur in these individuals can tell us about the time course and limits of such reorganization.

Methods

Subjects

Subjects were 12 right-handed, deaf adults (7 male, 5 female; average age = 29 years) and 10 right-handed hearing adults (5 male, 5 female; average age = 32 years) who had previously participated in a PET activation study of sign language processing (Petitto et al., 2000). All deaf subjects were profoundly congenitally deaf in both ears [average dB loss right ear = 95 (range = 90–110); average dB loss left ear = 94 (range = 88–110)], with no residual hearing and no known neurological deficits. In humans with congenital sensorineural hearing loss, agenesis of the inner and outer hair cells of the cochlea prevents sound waves from being transduced and transmitted to the auditory cortex. All deaf subjects were native speakers of a signed language (American Sign Language or Langue des Signes Québécoise) and had at least a high school education in that language. Control subjects were matched for linguistic proficiency and age. Subjects were drawn from the Montreal area population, were paid for their participation, and gave informed consent.

MRI scanning

MRI scans were performed on a Philips Gyroscan (1.5 T) using a 3D FFE acquisition sequence to collect 160 contiguous 1-mm thick, T1-weighted images in the sagittal plane (TR = 18 ms, TE = 10 ms). These data were automatically transformed into standardized stereotaxic space (Collins et al., 1994; Talairach and Tournoux, 1988). This resampling results in a volume of 160 1-mm slices with an in-plane matrix of 256 × 256. The stereotaxic transformation algorithm used applies three linear scaling factors, one for each spatial dimension, to each MRI volume (Collins et al., 1994). These scaling factors effectively normalize brain volume across subjects, controlling for differences in absolute brain volume, while preserving relative volume differences between individual hemispheres or brain regions.

Procedure

HG and PT were identified in each scan using landmarks (see Fig. 1) and criteria defined in previous studies (Penhune et al., 1996; Westbury et al., 1999). Based on careful review of the anatomical and physiological literature, HG was

defined as only the most anterior transverse gyrus on the superior temporal plane (for review of the relevant literature, see Penhune et al., 1996). Although there is no one-to-one correspondence between this gross anatomical definition and the cytoarchitectonic boundaries of primary auditory cortex, the tight coupling of mapping of this region from MRI (Penhune et al., 1996) and the extent of primary auditory cortex identified using quantitative cytoarchitecture techniques (Rademacher et al., 2001), make it a very good approximation (Patterson et al., 2002). Based on the work of Westbury et al. (1999) the PT was measured as the volume of the cortical ribbon lying behind HG and extending to the end of the Sylvian fissure. This includes the temporal-parietal extension of the Sylvian plane that is sometimes referred to as the planum parietale (Jancke et al., 1994). Measurement of the PT using this definition does not produce the commonly observed L > R asymmetry of the region, although this difference is still present if more traditional criteria are used (Westbury et al., 1999). Because there is controversy surrounding the definition of PT boundaries and whether the well-known asymmetry of the region is one of shape or volume (Binder et al., 1996; Loftus et al., 1993), we examined both the total volume and the angulation of the region in an effort to capture both aspects of asymmetry.

Raters were blind to subject group and hemisphere (scans were coded numerically and half were randomly selected and flipped around the x-axis). The MRI scans were viewed and labeled using DISPLAY, an interactive 3D imaging software package developed at the McConnell Brain Imaging Center at the Montreal Neurological Institute (MacDonald et al., 1994). DISPLAY allows scans to be viewed simultaneously in three planes of section, a feature that is vital in identifying the borders of HG and PT from two-dimensional slices. Overall intensity of the scans was set by visual inspection to give adequate grey/white contrast. The total volume of each region was labeled by marking all voxels in each continuous slice. For HG, both grey and white matter was labeled, for PT only grey matter was labeled. HG and PT were labeled separately in each hemisphere, and the labels were stored as locations in stereotaxic space. The resulting label volumes were used to create the 3D probability maps, to measure average location, and to calculate volumes. To assess reliability, two independent raters labeled a subset of scans for HG (RC and VP) and PT (RC and RDP).

Data analysis

Estimates of grey matter volume for the PT and of grey and white matter volumes for HG were obtained for each hemisphere by multiplying the number of marked voxels in each hemisphere by the MRI voxel dimensions (1 mm^3). Two methods of classifying grey and white matter volumes of HG were used: a rater-guided technique (Penhune et al., 1996) and an automatic tissue classification technique (Zijdenbos et al., 1996). In the rater-guided method, the histogram of MRI intensities across the full brain volume

was generated. The grey/white boundary for the scan was calculated from the histogram by identifying the peak intensity values corresponding to grey and white matter, and taking the midpoint. HG label volumes were then segmented, so that voxels with intensity values below the boundary were labeled as grey matter and those with intensity values above the boundary were labeled as white matter. Importantly, the grey/white border generated by this segmentation showed excellent correspondence with the border as visually identified from the scan. For the automatic technique, MRI scans were submitted to an automatic tissue classification algorithm that uses an artificial neural network classifier (Zijdenbos et al., 1996). The results of this classifier are binary grey matter, white matter, and CSF masks. These masks were then applied to the label volumes to segment grey matter and white matter and to exclude any voxels identified as CSF. For each technique, separate volumes were then calculated for HG grey- and white-matter regions. An index of asymmetry $\Delta = (R - L)/(R + L)/2$ was calculated for each region and tissue type. An index value was considered to be asymmetric when $\Delta \geq 0.10$. Interrater reliability was examined for each pair of raters for the two regions. To examine the location of HG and PT in the two groups, label volumes for each region were averaged across voxel location to produce 3D statistical probability maps. These maps provide a qualitative representation of the degree of variability in location and extent of the given region. In addition, the minimum and maximum x, y, and z values for each region were compared across groups and between hemispheres. The angulation of the PT in the left and right hemispheres was assessed by calculating the slope based on these minimum and maximum values [z extent/$\sqrt{(x \text{ extent}^2 + y \text{ extent}^2)}$].

In addition to manual labeling, a voxel-based statistical analysis (Ashburner and Friston, 2000) was used. This technique allows comparison of the relative density of grey and white matter across the whole brain between the two groups. For this analysis, the grey and white matter volumes generated by the automatic classification algorithm were smoothed using a 10-mm Gaussian filter and then compared on a voxel-by-voxel basis for the two groups resulting in t-statistic maps for the two tissue types (Worsley et al., 1996). A threshold of $t > 5.6$ was set for grey matter (5400 mm^3 search volume) and $t > 5.7$ for white matter (8100 mm^3 search volume; for both analyses: $P < 0.05$; $df = 20$, voxel size = 1 mm^3, 10 mm smoothing, and a volume of 540 cm^3).

Results

Volume measurements

Measurements of HG (see Fig. 2 and Table 1) showed preserved cortical grey and white matter volumes for the deaf compared to the hearing group [$F_{(1,20)} = 0.13$, $P >$
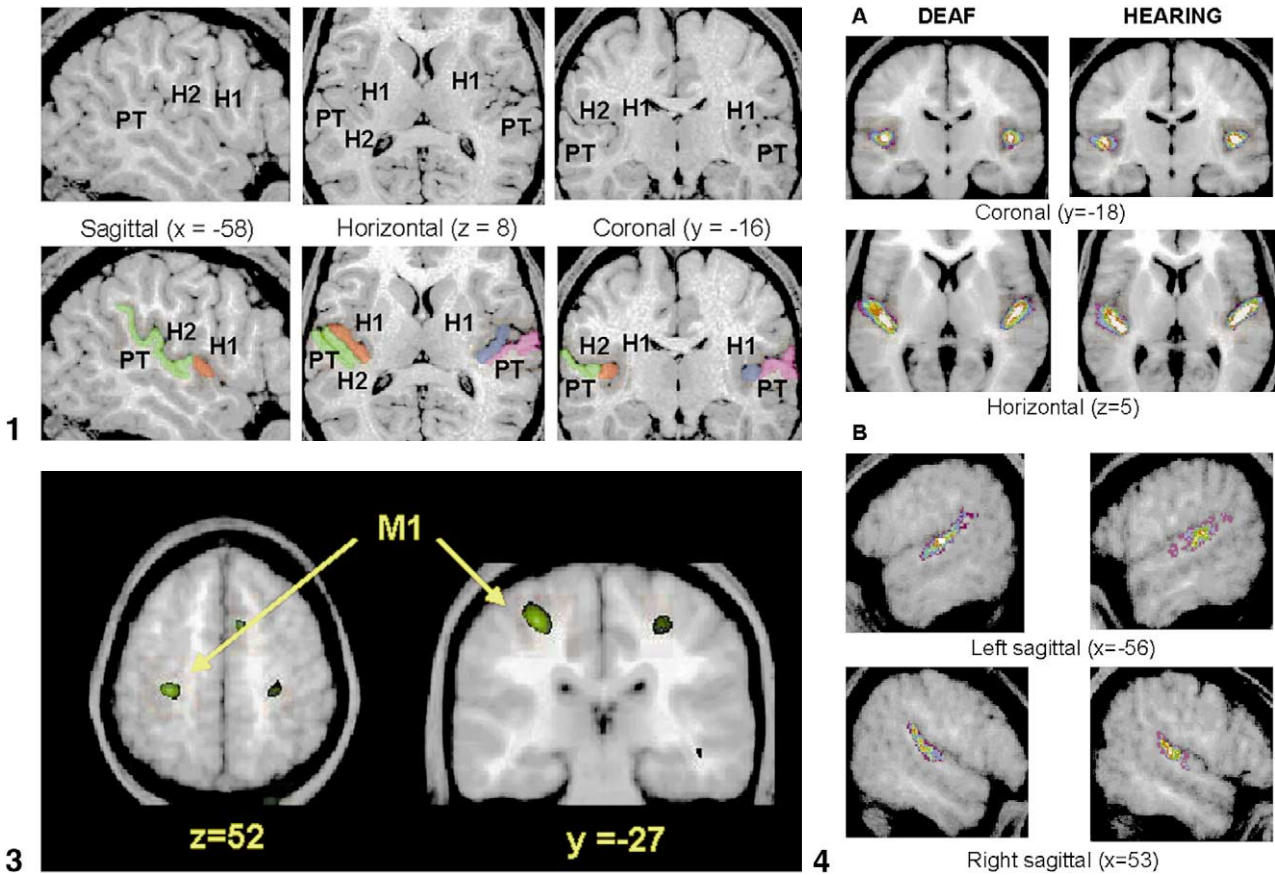
Fig. 1. This figure illustrates the labeling for HG and PT in the MRI scan of a single deaf subject. The sagittal, horizontal, and coronal planes of section are shown from left to right. The upper panel shows the unlabeled scan, the lower panel shows the labeled regions. In all images, left is left and right is right.

Fig. 3. Results of the voxel-based analyses of grey matter density showing the region of maximum difference located in the left motor hand area (M1) in horizontal ($z = 52$) and coronal ($y = -27$) slices. Of note in both images is a subthreshold region of difference located in right M1.

Fig. 4. This figure shows the probability maps of HG and PT for the two groups. Areas of highest probability (75–100%) are shown in white. For HG, note the similarity in location, extent, and variability of the maps for both groups. For PT, note the steeper slope of the right compared to left PT.

0.05]. Further, the distributions of HG volumes of the deaf and hearing groups in this sample were overlapping with those obtained in a previous sample (Penhune et al., 1996) of 20 hearing subjects [$F_{(2,38)} = 0.7$, $P > 0.05$]. When the deaf subjects were compared to a combined sample of the current matched controls plus the previous sample, the volumes were again entirely overlapping [$F_{(1,39)} = 0.96$, $P > 0.05$]. The mean of the deaf subjects was nonsignificantly larger than that of the combined hearing sample ($L_{deaf} = 2771$ mm^3, $L_{hearing} = 2618$ mm^3; $R_{deaf} = 2291$ mm^3, $R_{hearing} = 1978$ mm^3), and HG volumes for all deaf subjects fell within 1 SD of the mean (z scores for the smallest left and right HG were -1.02 and -0.70, respectively). Given the power of our present sample, differences of 17.2% in the total volume of HG could have been detected. Importantly, the predicted $L > R$ asymmetry in total HG volume was observed for both the deaf and matched hearing controls [$F_{(1,20)} = 13.08$, $P < 0.01$], with no difference in the index of asymmetry between the two groups for either grey matter, white matter, or total volume [$F_{(1,20)} = 0.7$, $P > 0.05$]. For these groups, both grey and white matter were larger on

the left ($t_{grey} = 0.03$; $t_{white} = 0.001$), but nonparametric analyses of the index of asymmetry for grey and white matter showed a significant effect such that the leftward asymmetry was larger for white matter than grey matter (Wilcoxon $z = -1.9$; $P = 0.03$, one-tailed).

PT measurements (see Fig 2 and Table 2) also showed complete preservation of cortical volume for the deaf compared to the hearing group [$F_{(1,20)} = 1.2$, $P > 0.05$]. Nor did PT volumes for either group differ from those obtained from a previous sample (Westbury et al., 1999) of 50 normal subjects [$F_{(2,68)} = 0.75$, $P > 0.05$]. When the deaf subjects were compared to a combined sample of the current matched controls plus the previous sample, the volumes were again entirely overlapping [$F_{(1,69)} = 0.46$, $P > 0.05$]. The mean of the deaf subjects was nonsignificantly smaller than that of the combined hearing sample ($L_{deaf} = 4135$ mm^3, $L_{hearing} = 4199$ mm^3; $R_{deaf} = 3765$ mm^3, $R_{hearing} = 4106$ mm^3), but PT volumes for all deaf subjects fell within 2 SD of the mean (z scores for the smallest left and right PT were -0.97 and -1.35, respectively). Given the power of our present sample, differences of 9.8% in the total volume of

the PT could have been detected. In the previous sample, no interhemispheric difference in the volume of PT was found. However, in the present study there was an overall L > R difference in PT volumes [$F_{(1,20)} = 5.8$, $P < 0.05$], that was significant for the hearing [$t_{(1,9)} = 4.2$, $P < 0.002$], but not the deaf group [$t_{(1,11)} = 0.8$, $P > 0.05$]. In this respect, the pattern of results for the deaf group in this sample was more similar to that of the hearing subjects in the previous sample.

The pattern of results was the same for the rater-guided and the automatic tissue classification methods, with the exception that the automatic method resulted in overall smaller volumes than the rater-guided method. This was expected because the automatic classification excludes voxels identified as CSF as well as segmenting grey and white matter. Three subjects (one deaf, two normal) had to be excluded from analysis for the automatic technique because inhomogeneity in the MRI data resulted in poor segmentation of grey and white matter. This inhomogeneity could be compensated for in the rater-guided technique. Therefore, to preserve a larger sample size and for comparability with the results of our previous studies, the results described above are from the rater-guided classification method. Interrater reliability for the volume measures of the two regions was excellent. The correlation between the two raters for total HG volume was 0.84 (R = 0.92; L = 0.79). The correlation for total PT volumes was 0.86 (R = 0.84; L = 0.83). These values are similar to those obtained in previous samples (Penhune et al., 1996; Westbury et al., 1999). Importantly, values of the index of asymmetry were also highly correlated for HG ($r = 0.91$) and PT ($r = 0.78$).

Voxel-based analyses

The results of the manual volume measurements for HG and PT were supported by the whole-brain voxel-based analysis that showed no significant differences between the deaf and hearing groups in any region of auditory cortex or in frontal or parietal language areas (see Fig. 3). Interestingly, the most significant difference between the groups ($t = 4.7$, $P < 0.001$, uncorrected; $P < 0.12$, corrected) revealed a greater density of grey matter relative to white matter in M1 of the deaf ($x = -30$, $y = -27$, $z = 52$). Although not significant after correction for multiple comparisons, this peak difference is located within 1 SD of the location identified for finger movement in an fMRI study comparing finger, tongue, and toe movements within motor cortex (Stippich et al., 2002). A very weak region of difference ($t = 2.9$) was also seen at a very similar location in right M1 ($x = 28$, $y = -27$, $z = 50$).

Probabilistic mapping

Probabilistic mapping of HG and PT showed a high degree of similarity in the location, extent, and variability of the region between deaf and hearing subjects (see Fig. 4).
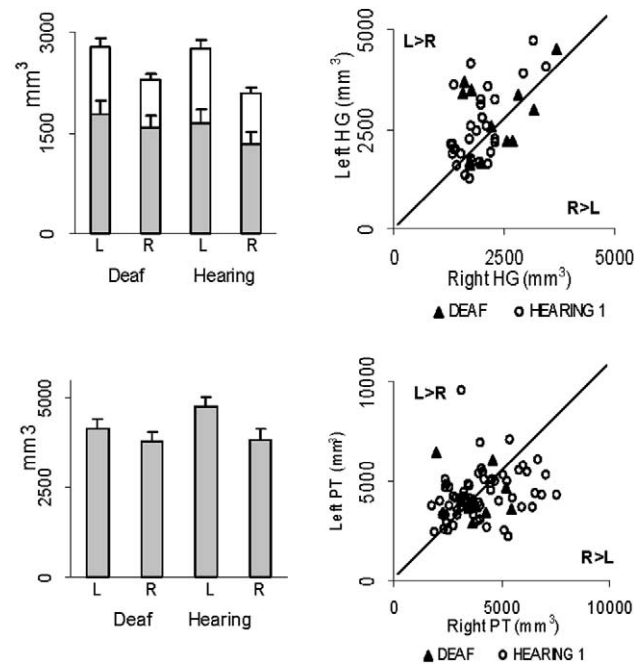

Fig. 2. These graphs illustrate the left and right HG (top) and PT (bottom) volumes for the deaf and hearing. The graphs on the left show the average volumes of left and right HG and PT. Grey bars indicate grey matter volumes, white bars indicate white matter volumes. Measurements of the total volume of HG and PT, and the grey and white-matter volume of HG are completely overlapping for the two groups. For HG, grey and white matter volumes were significantly larger on the left in both groups. The graphs on the right plot the total left and right volumes (mm³) of HG or PT for the deaf group (filled triangles) and the combined matched control and previous hearing groups (unfilled circles; $N_{HG} = 30$, $N_{PT} = 60$). The solid line represents the values for which left and right volumes would be equal. Points falling above the line are individuals who have L > R and those falling below the line have R > L.

For both groups, the region of highest probability (75–100%) was similar in extent and there appears to be greater variability in the lateral boundary of the left hemisphere than the right. For the PT, the region of highest probability was smaller, but similar for both groups.

A quantitative comparison of the location and extent of HG and PT between groups was made by extracting the minimum and maximum x, y, and z coordinates for each region in the two hemispheres (see Tables 3 and 4). For HG, there were no significant differences between the two groups [$F_{(1,17)} = 0.67$, $P > 0.05$]. Consistent interhemispheric differences were observed in both groups [$F_{(1,20)} = 6.3$, $P < 0.02$] in the posterior commencement of HG, such that right HG was located an average of 2 mm medial, anterior, and superior to left HG. This is consistent with the findings in our previous sample of hearing subjects showing an anterior shift in right HG (Penhune et al., 1996).

Comparison of the minimum and maximum x, y, and z coordinates for the PT showed a significant main effect of group [$F_{(1,20)} = 7.6$, $P < 0.01$], such that the inferior boundary of right PT was 4 mm lower in the deaf than the hearing group. Consistent interhemispheric differences

Table 1
HG volumes and indices of asymmetry (mm^3)

	Grey matter					White matter					Total			
	R	L	ASM	Classification		R	L	ASM	Classification		R	L	ASM	Classification
Deaf														
	1246	2647	−0.72	L		325	749	−0.79	L		1571	3396	−0.73	L
	1408	1246	0.12	R		313	345	−0.10	E		1721	1591	0.08	E
	466	863	−0.60	L		1257	838	0.40	R		1723	1701	0.01	E
	1630	1254	0.26	R		929	930	0.00	E		2559	2184	0.16	R
	2812	2781	0.01	E		866	1706	−0.65	L		3678	4487	−0.20	L
	1841	1458	0.23	R		1344	1525	−0.13	L		3185	2983	0.07	E
	1319	1111	0.17	R		658	534	0.21	R		1977	1645	0.18	R
	1569	1750	−0.11	L		635	815	−0.25	L		2204	2565	−0.15	L
	2102	1466	0.36	R		596	734	−0.21	L		2698	2200	0.20	R
	1168	2057	−0.55	L		439	1612	−1.14	L		1607	3669	−0.78	L
	1233	2533	−0.69	L		532	942	−0.56	L		1765	3475	−0.65	L
	2102	2249	−0.07	E		705	1102	−0.44	L		2807	3351	−0.18	L
avg	1575	1785	−0.1325		avg	717	986	−0.31		avg	2291	2771	−0.17	
sd	593	652	0.39964		sd	331	427	0.43		sd	690	931	0.36	
Hearing														
	2088	1991	0.05	E		1377	2057	−0.40	L		3465	4048	−0.16	R
	364	967	−0.91	L		958	1142	−0.18	L		1322	2109	−0.46	L
	1339	1641	−0.20	L		551	783	−0.35	L		1890	2424	−0.25	L
	2370	3198	−0.30	L		806	1533	−0.62	L		3176	4731	−0.39	L
	1405	1761	−0.22	L		602	1012	−0.51	L		2007	2773	−0.32	L
	1476	1665	−0.12	L		842	1550	−0.59	L		2318	3215	−0.32	L
	1540	1716	−0.11	L		583	843	−0.36	L		2123	2559	−0.19	L
	410	1014	−0.85	L		1014	990	0.02	E		1424	2004	−0.34	L
	1253	1170	0.07	E		514	553	−0.07	E		1767	1723	0.03	E
	985	1366	−0.32	L		365	509	−0.33	L		1350	1875	−0.33	L
avg	1323	1649	−0.291		avg	761	1097	−0.339		avg	2084	2746	−0.273	
sd	635	642	0.3364		sd	300	488	0.21137		sd	734	986	0.139	

were observed for both groups [$F_{(1,20)} = 18.7$, $P < 0.001$], such that right PT was located an average of 1 mm lateral and 3 mm superior to left PT. In addition, while the anterior borders of left and right PT did not differ, right PT was an average of 9 mm shorter in anterior-posterior extent. This is consistent with the findings in our previous sample of hearing subjects showing that the right PT was an average of 7 mm shorter in the anterior-posterior extent (Westbury et al., 1999).

The slope of the PT, a measure of the degree of angulation of the region, was also measured. Analysis of this variable revealed a significant group difference [$F_{(1,20)} = 6.7$, $P < 0.01$], but no interaction with hemisphere. Paired sample t tests for each group showed a trend for deaf subjects to have a more steeply sloped PT in the right than in the left hemisphere [$t_{(1,11)} = 2.0$, $P < 0.07$], whereas hearing subjects showed no difference between hemispheres [$t_{(1,9)} = 0.22$, $P > 0.05$]. In the previous sample of 50 hearing subjects examined in our laboratory, analysis of slopes showed a significantly steeper slope for the right than the left PT [$t_{(48)} = 2.7$, $P < 0.05$] (Westbury et al., 1999). Therefore, the pattern of PT slope results for the deaf subjects in the present sample is more similar to that of the normal hearing subjects in the previous study.

Discussion

The results of this study are striking in showing preservation of cortical volume in HG and PT of deaf subjects deprived of auditory input since birth. Measurements of grey and white matter, as well as the location and extent of these regions in the deaf, showed complete overlap both with matched controls and with two previous samples of hearing subjects. Most importantly, expected L > R differences in the volume of HG and in the angulation of the PT that are hypothesized to be related to auditory language processing were preserved in these deaf subjects. Finally, the results of the manual labeling were confirmed by a voxel-based statistical analysis that showed an increased grey-matter density in the motor cortex of the deaf, but no differences in any auditory cortical region.

The integrity of grey and white matter volumes of HG and PT in the deaf indicates no large-scale atrophy or degeneration as a result of complete, long-term auditory deprivation. This was confirmed by the automatic voxel-based analyses, which showed neither significant global differences in cortical volume between deaf and hearing groups nor specific differences in auditory regions. Cell loss following deprivation might have been expected as the

Table 2
PT volumes and indices of asymmetry (mm^3)

	Grey Matter			
	R	L	ASM	Classification
Deaf				
	3122	3977	−0.24	L
	2316	3403	−0.38	L
	3840	3737	0.03	E
	3700	4026	−0.08	E
	4274	3425	0.22	R
	3651	2875	0.24	R
	2005	6447	−1.05	L
	5226	4665	0.11	E
	4614	6042	−0.27	L
	5482	3532	0.43	R
	3474	3625	−0.04	E
	3475	3867	−0.11	E
avg	3765	4135	−0.10	
sd	1039	1078	0.38	
Hearing				
	3483	3959	−0.13	E
	3310	4446	−0.29	L
	3962	5334	−0.30	L
	3969	3875	0.02	E
	3481	4775	−0.31	L
	2824	4179	−0.39	L
	6008	5770	0.04	E
	4177	5443	−0.26	L
	4246	5076	−0.18	L
	2618	4680	−0.57	L
avg	3808	4754	−0.237	
sd	946	648	0.18391	

result of degeneration or accelerated pruning due to lack of auditory input. Previous studies in postnatally deafened animals and humans have shown changes in the volume of cells in auditory brainstem nuclei (Moore et al., 1997; Shepherd et al., 1997), but none have examined auditory cortex. Given the power, and the present sample size, atrophy in the range of 10–20% of total volume should have been detectable. This is well within the range of a recent volumetric MRI study showing increases in grey matter volume of 130% in musicians compared to nonmusicians (Schneider et al., 2002). If an environmental influence such as musical training, occurring relatively late in auditory cortical development, can produce this degree of change, it seems reasonable to predict that complete elimination of auditory input should produce changes of at least a similar magnitude. Conversely, the absence of gross morphological changes detectable with MRI does not exclude likely changes in cellular function and connectivity similar to those observed in neonatally deafened cats (Klinke et al., 1999; Kral et al., 2000; Wurth et al., 1999). The preservation of gross anatomical structure observed in the deaf demonstrates a preserved neural substrate that may be modified substantially in terms of its functionality.

The overlap in HG and PT volumes for the deaf and hearing found using manual labeling was confirmed by voxel-based analysis, where the only region nearing significance showed increased grey-matter density in the left motor hand area of the deaf. Increased density of grey

Table 3
Minimum and maximum *x*, *y*, and *z* coordinates for HG

	Left							Right					
	X_{min}	X_{max}	Y_{min}	Y_{max}	Z_{min}	Z_{max}		X_{min}	X_{max}	Y_{min}	Y_{max}	Z_{min}	Z_{max}
Deaf	36	63	−35	7	1	19		38	56	−28	2	−5	20
	31	66	−36	−8	6	19		33	65	−30	−12	6	20
	31	51	−32	−5	3	20		33	57	−30	−1	1	20
	28	58	−36	−14	6	17		35	70	−32	−4	3	18
	31	65	−33	−2	−3	19		31	69	−35	0	1	19
	31	64	−36	−3	2	16		34	62	−32	5	−2	17
	35	63	−33	2	2	14		35	61	−33	−3	2	16
	33	64	−31	3	1	18		34	59	−33	−2	3	19
	30	55	−28	0	1	14		32	58	−28	7	−1	15
	32	66	−28	1	−7	15		35	63	−29	0	−2	9
	29	64	−32	−4	−1	17		32	61	−29	−2	0	19
	32	65	−34	−2	4	19		33	70	−32	−10	5	20
Hearing	31	62	−34	−2	−5	19		35	69	−29	−1	0	17
	28	60	−35	0	3	17		34	66	−30	−9	8	18
	29	64	−33	8	−2	14		32	65	−32	0	3	15
	29	67	−39	−12	1	21		31	69	−30	1	3	18
	31	60	−33	1	0	15		35	59	−30	−2	0	16
	34	66	−25	9	−8	16		32	67	−35	−6	−3	17
	30	59	−33	−5	−2	20		30	64	−31	−3	−1	20
	30	65	−34	−2	3	17		35	60	−30	−8	6	16
	31	58	−28	2	0	15		32	62	−28	3	2	16
	32	57	−31	−1	2	12		33	63	−31	−8	6	15
avg	31	62	−33	−2	0	17	avg	33	64	−31	−3	2	17
sd	2.1	4.2	3.2	5.7	3.7	2.4	sd	1.8	4.3	2.0	4.9	3.3	2.6

Table 4
Minimum and maximum x, y, and z coordinates and slopes for PT

	Left								Right						
	X_{min}	X_{max}	Y_{min}	Y_{max}	Z_{min}	Z_{max}	Slope		X_{min}	X_{max}	Y_{min}	Y_{max}	Z_{min}	Z_{max}	Slope
Deaf	42	69	−52	−3	−5	26	0.55		42	69	−36	6	−1	27	0.69
	38	69	−44	−13	3	31	0.64		37	69	−40	−13	−1	23	0.57
	33	69	−51	−13	4	24	0.38		36	70	−40	−11	0	45	1.01
	35	70	−45	−20	−2	29	0.72		40	73	−42	−11	−5	40	0.99
	38	71	−47	−10	−2	17	0.38		37	71	−44	−17	0	33	0.76
	36	69	−42	−14	0	17	0.39		40	70	−38	−8	−3	31	0.80
	40	70	−60	−4	−1	29	0.47		40	72	−37	−5	1	17	0.35
	39	72	−45	−5	−2	36	0.73		39	72	−43	−3	0	29	0.56
	33	69	−49	−1	0	41	0.68		37	69	−33	6	−1	33	0.81
	36	71	−35	−2	−12	17	0.60		31	73	−37	−2	0	28	0.51
	33	70	−50	−18	−2	25	0.55		35	70	−41	−5	4	23	0.38
	36	69	−53	−13	−1	32	0.64		35	72	−38	−14	3	30	0.61
Hearing	39	69	−51	−13	−5	24	0.60		39	69	−40	−10	1	17	0.38
	32	68	−54	−1	−8	25	0.52		38	68	−44	−9	5	36	0.67
	33	70	−58	−4	−9	24	0.50		34	70	−49	−6	1	22	0.37
	34	70	−57	−21	0	21	0.41		38	72	−39	−7	−1	20	0.45
	38	69	−40	3	−11	21	0.66		40	69	−41	2	0	24	0.49
	39	71	−38	7	−8	26	0.76		34	71	−46	−13	1	16	0.30
	32	71	−61	−12	4	28	0.38		31	71	−40	−7	−3	35	0.73
	31	67	−60	−10	0	35	0.57		33	67	−41	−6	2	27	0.51
	33	69	−48	−1	−3	21	0.41		32	69	−40	−6	−1	20	0.42
	37	70	−42	−3	−8	23	0.61		35	70	−38	−10	0	19	0.42
avg	35	70	−49	−8	−3	26	0.55	avg	36	70	−41	−7	0	27	0.58
sd	3.1	1.1	7.4	7.5	4.6	6.3	0.1	sd	3.2	1.6	3.5	6.0	2.2	7.8	0.2

matter could result from increased cell size or number in the region. Because all of the subjects were right handed, this change in volume is likely to be related to extensive fine-motor use of the right hand while signing. While both hands are used during normal signing, the dominant hand is used more actively and generally executes the more motorically complex component of any sign (Brentari, 1999). This result is comparable to the results of voxel-based analyses showing use-dependent increases of grey matter volume in the motor cortex of musicians (Schlaug, 2001) and in the hippocampus of taxi drivers (Maguire et al., 2000).

In addition to the absence of global changes in morphology, we also replicated previously observed asymmetries of auditory cortex. Both the expected L > R asymmetry of HG volume and the greater angulation of the PT were preserved in deaf individuals. Some of these gross morphological asymmetries, along with asymmetries in cellular organization and function, have been hypothesized to be related to left-hemisphere dominance for language, or for processing of auditory features relevant for speech (Foundas et al., 1994; Galuske et al., 2000; Penhune et al., 1996; Westbury et al., 1999; Zatorre et al., 2002). The present results demonstrate that morphological asymmetries in the auditory cortex are preserved in the absence of auditory input, suggesting a strong genetic component in their development and maintenance. This is consistent with the finding of L > R asymmetry of the PT in the fetal brain (Witelson and Pallie, 1973), and with cytoarchitectonic studies showing

that auditory cortex matures through the first 6 months of life with little direct auditory input (Moore, 2002). Together with these studies, the present data indicate that auditory language experience is not required for the development or maintenance of auditory cortical asymmetries, suggesting that the possible substrates of auditory language function may be largely innate and not dependent on auditory experience. However, this does not negate the contribution of auditory or other types of linguistic experience in the development of potential functional asymmetries. Consistent with this idea, individuals with known right-hemisphere language lateralization show more variable asymmetry in HG, suggesting that auditory language processing can affect the expression of asymmetry (Dorsaint-Pierre et al., 2001). This is also consistent with data showing use-dependent changes in the volume of auditory cortex in professional musicians (Schneider et al., 2002). Importantly, while our findings support a strong genetic component to the development and maintenance of auditory cortical asymmetries, they cannot shed light on whether these asymmetries are language specific. Such interhemispheric differences may underlie more low-level auditory processing differences (Zatorre et al., 2002) that might facilitate the processing of auditory language, but might not be unique to language.

These results demonstrate the preservation of gross morphology of auditory cortex in deaf individuals, suggesting

possible functional reorganization. Supporting this hypothesis, a PET study in the same subjects showed that the PT was active in response to visual sign language stimuli (Petitto et al., 2000). Similar results have been obtained in other functional imaging studies of deaf subjects showing auditory cortical activation in response to sign language and other visual stimuli (Finney et al., 2001; Neville et al., 1998; Newman et al., 2002). Such cross-modal reorganization could occur through two potential routes that are not mutually exclusive. In the first route, lack of auditory input would result in reduced pruning of nonauditory input fibers, creating the potential for functional reorganization of auditory regions similar to that observed in animal preparations where auditory thalamic inputs are removed (Sur and Leamey, 2001). The second route for reorganization of auditory cortex would be through enhanced cortico-cortical connections from other sensory modalities. Both Rauschecker (1995) and Hamilton and Pascual-Leone (1998) have hypothesized that reorganization of visual cortex in blind animals and humans is the result of enhanced representation of somatosensory or auditory information arriving through normally existing connections from secondary and association areas. In the congenitally deaf, projections to auditory cortex from secondary visual and somatosensory areas and/or polymodal association areas could mediate reorganization.

Both pathways could result in an auditory cortex at least partially reorganized to process other types of sensory information. However, such reorganization is unlikely to be complete. Even in animal experiments where retinal output is surgically redirected to auditory cortex, structural and functional organization is not identical to normal visual cortex (Gao and Pallas, 1999; Ptito et al., 2001; Sharma et al., 2000) and visually guided behavior is limited (Frost et al., 2000; von Melchner et al., 2000). Based on work in "rewired" ferrets, Sur has described an interplay between early, genetically determined processes that govern macrostructural development and later, experience/input-dependent processes that guide microstructural development and functional connectivity (Sur and Leamey, 2001). This interplay between genetically and experientially determined factors might explain why reorganization in congenitally deaf cats and humans does not appear to be complete. In particular, this may explain why cochlear implants in humans and cochlear stimulation in animals are more effective at earlier ages, but remain at least partially effective later (Shepherd et al., 1997).

The result of auditory cortical reorganization could be that these regions process specifically language-related information, as suggested by the results of neuroimaging studies in deaf speakers of signed languages (Newman et al., 2002; Nishimura et al., 1999; Petitto et al., 2000). Conversely, the auditory cortex of deaf individuals may subserve more general-purpose processing from other modalities. In addition to linguistically relevant stimuli, auditory cortex has been shown to be active in response

to hand movements that are not perceived as meaningful signs (Petitto et al., 2000) and moving dot patterns (Finney et al., 2001). Further, there is no reason to assume that vacant auditory cortical real estate would be occupied only by visual input. In the case of the congenitally blind, visual cortex has been shown to respond to both tactile (Cohen et al., 1997) and auditory stimuli (Kujala et al., 1995; Weeks et al., 2000). Additional experiments contrasting linguistic and nonlinguistic stimuli and utilizing other sensory modalities are required to resolve these questions.

References

Anderson, B., Southern, B., Powers, R., 1999. Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. Neuropsychiatry Neuropsychol. Behav. Neurol. 12, 247–254.

Ashburner, J., Friston, K., 2000. Voxel-based morphometry—the methods. Neuroimage 11, 805–821.

Binder, J., Frost, J., Hammeke, T., Rao, S., Cox, R., 1996. Function of the left planum temporale in auditory and linguistic processing. Brain 119, 1239–1247.

Brentari, D., 1999. A Prosodic Model of Sign Language Phonology. MIT Press, Cambridge, MA.

Cohen, L., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Dambrosia, J., Honda, M., Sadato, N., Gerloff, C., Catala, M., Hallett, M., 1997. Functional relevance of cross-modal plasticity in blind humans. Nature 389, 180–183.

Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.

Dorsaint-Pierre, R., Zatorre, R.J., Penhune, V.B., 2001 Morphological asymmetries of the planum temporale and Heschl's gyrus: relationship to language lateralization. program no. 822.3 Abstract viewer/itinerary planner. Washington, DC: Soc. Neurosci.

Finney, E., Fine, I., Dobkins, K., 2001. Visual stimuli activate auditory cortex in the deaf. Nat. Neurosci. 4, 1171–1173.

Foundas, A., Leonard, C., Gilmore, R., Fennell, E., Heilman, K., 1994. Planum temporale asymmetry and language dominance. Neuropsychologia 32, 1225–1231.

Frost, D., Boire, D., Gingras, G., Ptito, M., 2000. Surgically created neural pathways mediate visual pattern descrimination. Proc. Natl. Acad. Sci. USA 97, 11068–11073.

Galaburda, A., LeMay, M., Kemper, T., Geschwind, N., 1978a. Right-left asymmetrics in the brain. Science 199, 852–856.

Galaburda, A. M., Sanides, F., Geshwind, N., 1978b. Cytoarchitectonic left-right differences in the temporal speech region. Arch. Neurol. 35, 812–817.

Galuske, R., Scholote, W., Bratzke, H., Singer, W., 2000. Interhemispheric asymmetries of the modular structural of human temporal cortex. Science 289, 1946–1949.

Gao, W.-J., Pallas, S., 1999. Cross-modal reorganization of horizontal connectivity in auditory cortex without altering thalamocortical projections. J. Neurosci. 19, 7940–7950.

Geschwind, N., Levitsky, W., 1968. Human brain: left-right asymmetries in the temporal speech region. Science 161, 186–187.

Hamilton, R., Pascual-Leone, A., 1998. Cortical plasticity associated with Braille learning. Trends Cogn. Sci. 2, 168–174.

Hari, R., Pelizzone, M., Makela, J. P., Hallstrom, J., Huttunen, J., Knuutila, J., 1988. Neuromagnetic responses from a deaf subject to stimuli presented through a multichannel cochlear prosthesis. Ear Hear 9, 148–152.

Heschl, R., 1878. Ueber die Vordere Quere Schläfenwidung des Menschlichen Grosshirns. Wilhelm Braumüller, Vienna, Austria.

Hirano, S., Naito, Y., Kojima, H., Honjo, I., Inoue, M., Shoji, K., Tateya, I., Fujiki, N., Nishizawa, S., Konishi, J., 2000. Functional differentiation of the auditory association area in prelingually deaf subjects. Auris Nasus Larynx 27, 303–310.

Jancke, L., Schlaug, G., Huang, Y., Steinmetz, H., 1994. Asymmetry of the planum parietale. Neuroreport 5, 1161–1163.

Klinke, R., Kral, A., Heid, S., Tillein, J., Hartmann, R., 1999. Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. Science 285, 1729–1733.

Kral, A., Hartmann, R., Tillein, J., Heid, S., Klinke, R., 2000. Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. Cereb. Cortex 10, 714–726.

Kujala, T., Huotilainen, M., Sinkkonen, J., Ahonen, A., Ahlo, K., Hamalainen, M., Ilmoniemi, R., Kajola, M., Knuutila, J., Lavikainen, J., 1995. Visual cortex activation in blind humans during sound discrimination. Neurosci. Lett. 183, 143–146.

Loftus, W., Tramo, M., Thomas, C., Green, R., Nordgren, R., Gazzaniga, M., 1993. Three-dimensional quantitative analysis of hemispheric asymmetry in the human superior temporal region. Cereb. Cortex 3, 348–355.

MacDonald, J., Avis, D., Evans, A., 1994. Multiple surface identification and matching in magnetic resonance images. Proc. Int. Conf. Visual. Biomed. Comput. 160–169.

Maguire, E., Gadian, D., Johnsrude, I., Good, C., Ashburner, J., Frackowiak, R., Frith, C., 2000. Navigation-related structural changes in the hippocampi of taxi drivers. Proc. Nat. Acad. Sci. USA 97, 4398–4403.

McMullen, N., Glaser, E., 1988. Auditory cortical responses to neonatal deafening: pyramidal neuron spine loss without changes in growth or orientation. Exp. Brain Res. 72, 195–200.

Moore, J., 2002. Maturation of human auditory cortex: implications for speech perception. Ann. Otol. Rhinol. Laryngol. 111 (5 Pt 2), 7–10.

Moore, J., Niparko, J., Miller, M., Perazzo, L., Linthicum, F., 1997. Effect of adult-onset deafness on the human central auditory system. Ann. Otol. Rhinol. Laryngol. 106, 385–390.

Morosan, P., Rademacher, J., Schleicher, A., Amunts, K., Schormann, T., Zilles, K., 2001. Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. Neuroimage 13, 684–701.

Naito, Y., Hirano, S., Honjo, I., Okazawa, H., Ishizu, K., Takahashi, H., Fujiki, N., Shiomi, Y., Yonekura, Y., Konishi, J., 1997. Sound-induced activation of auditory cortices in cochlear implant users with post- and prelingual deafness demonstrated by positron emission tomography. Acta Otolaryngol. 117, 490–496.

Neville, H., Bavelier, D., Corina, D., Rauschecker, J., Karni, A., Lalwani, A., Braun, A., Clark, V., Jezzard, P., Turner, R., 1998. Cerebral organization for language in deaf and hearing subjects: biological con-

straints and effects of experience. Proc. Natl. Acad. Sci. USA 95, 922–929.

Newman, A., Bavelier, D., Corina, D., Jezzard, P., Neville, H., 2002. A critical period for right hemisphere recruitment in american sign language processing. Nat. Neurosci. 5, 76–80.

Nishimura, H., Hashikawa, K., Doi, K., Iwaki, T., Watanabe, Y., Kusuoka, H., Nishimura, T., Kubo, T., 1999. Sign language "heard" in the auditory cortex. Nature 397, 116.

Okazawa, H., Naito, Y., Yonekura, Y., Sadato, N., Hirano, S., Nishizawa, S., Magata, Y., Ishizu, K., Tamaki, N., Honjo, I., Konishi, J., 1996. Cochlear implant efficiency in pre- and postlingually deaf subjects: a study with H_2O^{15} and PET. Brain 119, 1297–1306.

Patterson, R., Uppenkamp, S., Johnsrude, I., Griffiths, T., 2002. The processing of temporal pitch and melody information in auditory cortex. Neuron 36, 767–776.

Penhune, V.B., Zatorre, R. J., MacDonald, J.D., Evans, A.C., 1996. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb. Cortex 6, 661–672.

Petitto, L.A., Zatorre, R.J., Gauna, K., Nikelski, E.J., Dostie, D., Evans, A.C., 2000. Speech-like cerebral activity in profoundly deaf people processing signed languages: implications for the neural basis of human language. Proc. Natl. Acad. Sci. USA 97, 13961–13966.

Pfeifer, R.A., 1936. Pathologie der Hörstrahlung und der corticalen Hörsphäre, in: Bumke, O., Foerster, O. (Eds.), Handbuch der Neurologie, Vol. 6. Springer-Verlag, Berlin, pp. 533–636.

Ponton, C., Moore, J., Eggermont, J., 1999. Prolonged deafness limits auditory system developmental plasticity: evidence from an evoked potentials study in children with cochlear implants. Scand. Audiol. Suppl. 51, 13–22.

Ptito, M., Giguere, J., Boire, D., Frost, D., Casanova, C., 2001. When the auditory cortex turns visual. Prog. Brain Res. 134, 447–458.

Rademacher, J., Morosan, P., Schormann, T., Schleicher, A., Werner, C., Freund, H.-J., Zilles, K., 2001. Probabilistic mapping and volume measurement of human primary auditory cortex. Neuroimage 13, 669–683.

Rauschecker, J., 1995. Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci. 18, 36–43.

Reale, R.A., Brugge, J.F., Chan, J.C.K., 1987. Maps of auditory cortex in cats reared after unilateral cochlear ablation in the neonatal period. Brain Res. 431, 281–290.

Schlaug, G., 2001. The brain of musicians. A model for functional and structural adaptation. Ann. NY Acad. Sci. 930, 281–299.

Schneider, P., Scherg, M., Dosch, H., Specht, H., Gutschalk, A., Rupp, A., 2002. Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. Nat. Neurosci. 5, 688–694.

Seldon, H., 1982. Structure of human auditory cortex III: statistical analysis of dendritic trees. Brain Res. 249, 211–221.

Sharma, J., Angelucci, A., Sur, J., 2000. Induction of visual orientation modules in auditory cortex. Nature 404, 841–847.

Shepherd, R.K., Hartmann, R., Heid, S., Hardie, N., Klinke, R., 1997. The central auditory system and auditory deprivation: experience with cochlear implants in the congenitally deaf. Acta Otolaryngol. Suppl 532, 28–33.

Stippich, C., Ochmann, H., Sartor, K., 2002. Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. Neurosci. Lett. 331, 50–54.

Sur, M., Leamey, C., 2001. Development and plasticity of cortical areas and networks. Nat. Rev. Neurosci. 2, 251–262.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers, Inc., New York.

von Economo, C., Horn, L., 1930. Über Windungsrelief. Maβe und Rindenarchitektonik der Supratemporalfläche, ihre individuellen und ihre Seitenunterschiede. Z. Neurol. Psychiat. 130, 678–757.

von Melchner, L., Pallas, S., Sur, M., 2000. Visual behavior mediated by retinal projections directed to the auditory pathway. Nature 404, 871–876.

Weeks, R., Horwitz, B., Aziz-Sultan, A., Tian, B., Wessinger, C., Cohen, L., Hallett, M., Rauschecker, J., 2000. A positron emission tomographic study of auditory localization in the congenitally blind. J. Neurosci. 20, 2664–2672.

Westbury, C.F., Zatorre, R.J., Evans, A.C., 1999. Quantifying variability in the planum temporale: a probability map. Cereb. Cortex 9, 392–405.

Witelson, S., Pallie, W., 1973. Left hemisphere specialization for language in the newborn: neuroanatomical evidence of asymmetry. Brain 96, 641–646.

Worsley, K., Marret, S., Neelin, P., Vandal, A., Friston, K., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Neuroimage 2, 244–252.

Wurth, N., Heid, S., Kral, A., Klinke, R., 1999. Morphology of neurons in the primary auditory cortex (AI) i normal and congenitally deaf cats—a study of Dil labelled cells. Gottingen Neurobiol. Rep. 318.

Zatorre, R.J., Belin, P., Penhune, V.B., 2002. Structure and function of the human auditory cortex: music and speech. Trends Cogn. Sci. 6, 37–46.

Zijdenbos, A., Evans, A., Riahi, F., Sled, J., Chui, H.-C., Kollokian, V., 1996. Automatic quantification of multiple sclerosis lesion volume using stereotaxic space. Proc. Int. Conf. Visual. Biomed. Comput. 439–448.