Morphometric Differences in the Heschl’s Gyrus of Hearing Impaired and Normal Hearing Infants

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This study investigates the morphometry of Heschl’s gyrus and its included primary auditory cortex (PAC) in hearing impaired (HI) and normal hearing (NH) infants. Forty-two infants, age 8–19 months, with NH (n = 26) or hearing impairment (n = 16) were studied using high-resolution 3D magnetic resonance imaging. Gray matter (GM) and white matter (WM) volumes were obtained using software for automatic brain imaging segmentation to estimate the volume of each tissue within manually defined regions for the anterior portion of Heschl’s gyrus (aHG) in each individual subject, transformed to an infant brain template space. Interactions among group (HI, NH), tissue type (GM, WM), and hemisphere (left, right) were examined using analysis of variance. Whole-brain voxel-based morphometry was utilized to explore volume differences between groups across the entire brain. The HI group showed increased GM and decreased WM in aHG compared with the NH group; likely effects of auditory deprivation. The HI group did not exhibit their typical L > R asymmetry pattern that the NH group showed. Increased GM in aHG in HI infants may represent abnormal cortical development in PAC as seen in animal models of sensory deprivation. Lower WM volume is consistent with studies with deaf adults.

Keywords: auditory cortex, brain imaging, deaf, neurodevelopment, pediatric

Introduction

Children with congenital deafness are deprived of auditory stimulation during critical periods of brain and language development. Despite sound deprivation, there is still potential for auditory functionality as evidenced in cochlear implant recipients. Nevertheless, development of the central auditory system may be impeded in the absence of sound stimulation. This could in turn adversely affect recovery of function if auditory input is later restored with a hearing aid or cochlear implant. In this study, we examined the morphology of anterior Heschl’s gyrus (HG) as an estimate of primary auditory cortex (PAC), in deaf and normal hearing (NH) infants 8–19 months of age, using anatomical magnetic resonance imaging (MRI).

The timeline of the development of the PAC may provide insight into the potential effects of auditory deprivation from birth. The auditory system begins to develop shortly after conception through a genetically mediated process that guides the formation of cochlea, cochlear nerve, and the basic structure of the auditory brainstem and cortex (Moore and Linthicum 2007). At the beginning of the third trimester, the fetus begins to demonstrate physiological responses to sound. This timing parallels the appearance of myelin from the cochlea through the brainstem to the thalamus (Moore and Linthicum 2007). At this point, sound stimulation may be integral to the continued formation of the structures of the auditory system. Sound deprivation has been shown to alter the structure of the brainstem in animals, causing dendritic abnormalities during the perinatal period (Moore and Linthicum 2007). This period is characterized by axonal maturation in the brainstem and development of the PAC. In humans, HG becomes distinct from the superior temporal gyrus (STG) during the 37th week of gestation (Moore and Guan 2001). Although the basic structure of HG is present, dendrites, axons, and synapses are still maturing through birth up to 6 years and may be negatively impacted by sound deprivation. For example, shorter dendrites bearing fewer synaptic spines were found in animals deafened at birth (McMullen and Glaser 1988; McMullen et al. 1988). It is possible that the changes due to sound deprivation may affect the macroanatomic structure of HG in humans as well. As a primary sensory area, HG is one of the first areas of the brain to mature, leaving it more vulnerable to the effects of congenital deafness than higher order association areas which mature later, paralleling functional development (Gogtay et al. 2004).

Two studies to date have investigated the macroanatomic structure of HG in deaf adults (Emmorey et al. 2003; Penhune et al. 2003). Among them, there is no evidence that the total volume of HG is different due to deafness. There is also a consensus that gray matter (GM) is preserved in deaf subjects, indicating auditory deprivation does not cause extensive atrophy in HG and its included PAC. A white matter (WM) deficit was found by Emmorey et al. (2003) in the HG of both hemispheres in deaf compared with hearing adults. However, Penhune et al. (2003) found no WM differences between deaf and hearing adults. More recently, Shibata (2007), utilizing voxel-based morphometry (VBM) to examine whole brain WM and GM separately, observed a difference in the WM of the left superior temporal gyrus; with deaf adults having significantly less WM than NH adults. This area of WM decrease was described as potential auditory tracks leading to HG. Taken together, these prior studies suggest that adults, deprived of auditory stimulation from birth, may have some WM dysplasia in auditory cortical areas but have structurally intact GM and the overall volume of HG is not significantly impacted.

Hemispheric differences in HG have also been found, with a mixture of results generally showing a greater left auditory cortex compared with the right. Penhune et al. (1996) noted a hemispheric asymmetry of WM in hearing adults. A later study...
found both GM and WM were larger in the left for NH and HI adults (Penhune et al. 2003). Emmorey et al. (2003) noted a leftward asymmetry only for GM in both groups. A leftward asymmetry was also found in the cytoarchitecture of PAC in NH adults (Rademacher et al. 2001). Results are somewhat conflicting but indicate that deaf adults follow the same asymmetry pattern as hearing adults.

The purpose of this study was to assess volumetric and structural changes in anterior Heschl’s gyrus (aHG) due to congenital hearing impairment during infancy. This study and previous MRI studies have used HG to estimate the area of PAC; given that PAC can only be truly defined based on cytoarchitecture (Rademacher et al. 1993). It has been shown that the PAC is most frequently included in the anterior portion of HG (Rademacher et al. 1993; Penhune et al. 1996). Throughout this paper, we focus our attention on this region as it is the best macroanatomic landmark of PAC and we will consistently refer to our defined region as aHG (Schneider et al. 2002). Because the auditory system is still developing well after birth, investigating aHG in infants may provide unique insight into how and when the structure of the developing brain is influenced by auditory deprivation. To our knowledge, no volumetric studies have examined aHG in deaf children. We examined the total volume, GM, and WM volume of aHG in deaf and hearing infants using manual regions of interest (ROIs). Consistent with prior studies in adults, we hypothesized that there would be no difference in total volume or GM volume, but WM volume would be significantly decreased in deaf subjects. We also explored volume differences between groups over the entire brain using whole-brain VBM.

Materials and Methods

Subjects
All subjects included in this study were referred for a clinically indicated MRI scan. Because infants require sedation for MR imaging and we consider it unethical to sedate infants for research purposes only, the research protocol was added at the end of the clinical scan with Institutional Review Board approval. No participants were subjected to MRI with sedation solely for the purposes of this research study. Subjects included 42 infants, 8–19 months of age with NH (n = 26; 18 females, 8 males, mean age = 12 months, standard deviation [SD] = 2.6) or sensorineural hearing impairment (n = 16, 8 females, 8 males, mean age = 14 months, SD = 3.0). The difference in age between the NH and HI groups is significant (t = 2.3, P = 0.03). Therefore we included age as a regressor in all subsequent analyses. Subjects were sedated for clinical MRI scans using either Nembutal (5 mg/kg oral) or Propofol (200 mcg/kg/min intravenously). All subjects had a grossly normal brain MRI as evaluated by a pediatric neuroradiologist. NH subjects were recruited from the clinical MRI schedule and met inclusion criteria of gestational age of at least 36 weeks, normal otocochlear emissions hearing, and referral for nonhearing related reasons. The NH subjects were referred for an MRI of the brain for a variety of reasons; see Table 1 for a complete list. The NH children may have had underlying neurocognitive difficulties that lead to their referral. However, the referral pathways for the subjects varied from family pediatrician to subspecialist with concomitant variability in neurological and neurocognitive evaluations. Consequently, it is not possible to group these subjects into neurologically normal and abnormal subgroups; however, the brain MRI of all subjects was read as within normal limits.

The HI subjects had congenital hearing impairment in the severe to profound range (n = 15), with one patient (n = 1) in the moderate to severe range of hearing loss. All hearing impaired (HI) patients were undergoing evaluations for cochlear implantation at the time of recruitment and were referred for clinical MRI exams as part of the preoperative staging process. Two HI subjects, not included in the total number, were excluded because of poorly defined HG boundaries making it too difficult to trace. Written informed consent was obtained from the parent or guardian of each subject for their child to participate in the research study.

MRI Scan
High resolution 3D-T1, weighted anatomical images were obtained using a 3 T clinical MRI scanner in the Radiology Department of Cincinnati Children’s Hospital. These scans were acquired using an inversion recovery rapid gradient-echo 3D method (magnetization prepared rapid gradient echo [MP-RAGE]) covering the entire brain at a spatial resolution of 1 × 1 × 1 mm. Three-dimensional MP-RAGE acquisition parameters are as follows: time to inversion/time repetition/time echo = 1100/2000/23 ms, field of view = 21.9 × 21.9 cm, matrix = 256 × 256, scan time = 3 min and 50 s. This series of images was used for anatomical coregistration of MRI results acquired during the same imaging examination.

aHG Manual Measurement Procedure
Review of the relevant literature was used as a guide for defining the landmarks of aHG along with expertise of the pediatric neuroradiologists (M.K. and J.E.) and an expert in the neuroanatomy of auditory cortex (R.M.) involved in the study (Penhune et al. 1996; Maitra et al. 2009). aHG is defined as the first transverse gyrus of the temporal lobe. The PAC does not correspond perfectly to aHG based on cytoarchitecture, however, the medial two-thirds of the first transverse gyrus is generally considered to be the site of PAC (Rademacher et al. 2001). Given the high individual variability in aHG and the PAC, it may contain secondary auditory areas and may not contain the full extent of PAC. There are no precise macroanatomic landmarks to define PAC based on cytoarchitecture thus the first transverse temporal gyrus remains the best macroanatomic landmark for PAC (Penhune et al. 1996; Rademacher et al. 2001).

aHG is located on the middle superior surface of the STG. It is oriented in an anterolateral and postero medial direction. Anterolaterally, it fuses with the anterior portion of the STG and posteriorly it fuses with the insula. It is defined medially by the anterior transverse sulcus and laterally by Heschl’s sulcus (see Fig. 1). Duplicate HGs are common, so if more than one HG was present, only the most anterior HG was considered to include PAC, according to convention (Rademacher et al. 1993). Figure 1 also shows an example of a duplicate HG with the anterior HG labeled H1 in the figure. In cases when a sulcus intermedius (SI) was present and it divided HG by more than half (e.g., a common stem duplication), only the anterior portion of the gyrus was traced. In this case, the SI was considered the posterior boundary. In the case of a complete posterior duplication in which a fully separate gyrus is present, the sulcus in between the gyri is known as Heschl’s sulcus, and the sulcus lateral to the second gyri is called the second Heschl’s sulcus (Abdul-Kareem and Sluming 2008). Here, the first Heschl’s sulcus was the posterior boundary so that only the anterior most gyrus was included in the ROI.
ROIs were drawn manually, using the landmarks defined above, in the native space on contiguous coronal brain slices by 2 reviewers experienced in brain imaging (K.S. and M.M.) and a third reviewer who is a pediatric radiologist (M.K.). Raters were blinded to subject group. While marking landmarks, the anatomy was viewed concurrently in 2D coronal, axial, and sagittal orientations.

The ROI was drawn first using the procedure described below followed by automatic segmentation of GM and WM from within the ROI. Anterior HG was identified on the axial slice on which it could be best visualized, shown in the top panel of Figure 2. On this slice, the full extent of the anterior transverse sulcus and Heschl’s sulcus, defining the anterior and posterior boundaries of HG, were clearly visible. HG was further delineated from this initial slice in the following manner: 1) From this slice, we moved superiorly to the last axial slice in which the HG could be differentiated (see Step 1 in Fig. 2) and the most posterior-medial end of the gyrus was landmarked with a crosshair to mark the origin of HG. This location was confirmed in coronal and sagittal planes using the crosshair location projected into each plane. In the case of a common stem duplication in which there was one gyrus at the posteromedial end and a complete bifurcation at the lateral end, the point was marked at the most posterior-medial end of the most anterior gyrus. 2) We retraced aHG inferiorly on the axial plane to the last slice in which it could be differentiated from the superior temporal gyrus (as shown in Step 2 of Fig. 2) and marked the most anterolateral end of the gyrus with a crosshair to mark the end of aHG. This location was also confirmed on coronal and sagittal planes (see Fig. 2). 3) The inferior boundary of the ROI was defined by the roof of the WM of the STG as viewed in the coronal plane. In the case of a common stem duplication at the posterior end because the inferior boundary is defined in the coronal plane as described above, the common stem, as seen in the axial plane, is not included in the ROI. At the anterior end, as the Heschl’s sulcus reached the lateral border of STG, only the edge of the GM of aHG superior to level of WM of STG was included in the ROI. Hence, the most lateral extent of WM of STG was defined as the lateral boundary of aHG (Hirayasu et al. 2000).

Figure 3 demonstrates one slice of the ROI for aHG in 3 orthogonal planes. Three-plane image display, landmarking, and ROI drawing were all done using software written in-house in Interactive Data Language (ITT Visual Information Solutions) and used extensively in our laboratory (http://irc.cchmc.org/software/cchips.php). Images are displayed in radiological orientation.

**Interrater Reliability**

Three independent raters traced ROIs encompassing aHG in left and right hemispheres separately for all subjects. Volumes estimated from each reviewers ROI were tested for consistency using intraclass correlation. The interclass correlation coefficient (ICC) was calculated for the left aHG ROI (ICC = 0.95) and for the right aHG ROI (ICC = 0.95) (Shrout and Fleiss 1979; McGraw and Wong 1996).

Occasionally individual raters had difficulties identifying posterior duplications in specific subjects. In these cases, the raters viewed the gyri together and came to a consensus on the boundary of the anterior gyrus and traced aHG accordingly. The classification of a second posterior gyrus could affect the number of duplicated gyri, but since we report only the volume of the most anterior gyrus, posterior duplications do not affect the primary analyses of this paper. The number of duplications is reported by percent of gyral duplications that
includes both common stem duplications and complete posterior duplications, in each hearing group and hemisphere. In the HI group, 38% of the gyri were duplicated in both the left and right hemispheres. For the NH group, 19% of gyri in the left hemisphere and 46% of the gyri in the right hemisphere were duplicated.

### Data Analysis

Automated segmentation of GM, WM, and cerebrospinal fluid was performed in Statistical Parameter Mapping (SPM5) software (Welcome Department, University College, London, UK). We used the approach of Ashburner and Friston that minimizes an objective function to estimate tissue classification with bias correction and image registration (Ashburner and Friston 2005). However, to avoid biases that could be introduced by using adult prior templates to weight the voxel classification process, we used an infant brain template and a priori data based on high-quality T1-weighted 3 T magnetic resonance (MR) images from 76 infants whose age ranged from 9 to 15 months (Altaye et al. 2008). We utilized the unified segmentation procedure implemented in SPM5 environment but modified it to include a Hidden Markov Random Field model as an additional spatial constraint (Cuadra et al. 2005). We then applied the normalization parameters obtained during the segmentation process to the manually drawn ROI of each infant. We finally overlaid the normalized ROI on the modulated and segmented brain to extract the estimates for GM and WM volumes within the left and right aHG ROI for each subject.

Given the excellent reliability among raters, ROIs from a single rater (K.S.) were used for volume extraction of GM and WM volumes within the defined ROI. In addition to estimating the total GM and WM volume, we also calculated a gray to white matter volume ratio (GM/WM). We initially performed a 3-way analysis of variance where tissue type (GM, WM) and hemisphere (left, right) were treated as within-subject variables and hearing status (HI, NH) as a between-subject variable. This model was fitted using SAS PROC Mixed procedure version 9.2 (SAS Institute Inc.). Based on the result of this initial analysis, we then performed comparisons between hearing groups, hemispheres, or tissue types using 2-sample and paired t-tests as appropriate. Since the size of the ROI may differ from infant to infant during this period of rapid brain development, the between-subject variations in the total GM and WM volume tend to be large. Therefore instead of using the observed mean to do the comparison, we used the least square means that were generated from a mixed model regression. We modeled the volumes as a function of hearing groups but controlling for total brain size, as well as gender and age since both variables seem to have different distributions for each group. We then used the resulting least square means (adjusted means) and their standard error to conduct the subsequent t-tests. All reported P values for the mean comparisons are adjusted for the number of multiple tests using a false discovery rate (FDR) method. FDR is a statistical method used for adjusting for multiple testing by controlling the expected proportion of incorrectly rejected null hypothesis (Benjamini and Hochberg 1995; Penhune et al. 2003).

### Whole-Brain VBM

Whole-brain VBM was utilized to explore GM and WM volumetric differences between hearing groups across the entire brain. For this analysis, we used the modulated and normalized GM and WM images. Prior to statistical analysis, we smoothed these images using a Gaussian filter with 8 mm full-width half-maximum via SPM5 in order to reduce the anatomical variability and to improve the signal to noise ratio. We then used a general linear model approach to compare the volumetric difference between hearing groups. In this setting, the smoothed image volumes were modeled as a function of hearing group and potential confounder variables: age, sex, and total brain volume. In this level analysis, we worked with brain images transformed back into the native space so that differences could be computed in absolute volumes (mm$^3$) rather than percentages.

### Results

The mixed model analysis indicated that there was not a 3-way [hemisphere (left, right) by hearing status (HI, NH) by tissue type (GM, WM)] interaction (P = 0.40). Subsequently, we removed the 3-way interaction term and refit the model. In this reduced model, all 3 two-way interactions terms were significant (hearing status by tissue type, P = 0.03; hearing status by hemisphere, P = 0.02; tissue type by hemisphere, P = 0.001). Because of the significance of these interaction terms subsequent analysis was performed by splitting the data along one of the interaction variable and conducting 2-sample and paired t-tests as appropriate.

Total, GM, and WM volumes within the aHG ROI by hearing status are presented in Table 2. Similar to previously reported adult studies, the total left and right volumes of HG were not significantly different between the HI and NH infant groups. However, the segmentation of aHG revealed differences between the groups in both GM and WM. There was a significant difference in volume, with the HI group having less WM (P = 0.030) and more GM (P = 0.038) than the NH group. P values listed in Tables 2–4 are all corrected for multiple comparisons. Decreased WM in the HI group is consistent with previous studies, however, increased GM has not been observed in prior studies of deaf individuals. The higher GM and lower WM in the HI infants are also consistent with the significantly higher GM/WM ratio (P = 0.0007) compared with the NH group.

The HI group was not homogeneous in terms of comorbid neurological findings. To further investigate the effect of neurological status on our results, we separated the HI group into 3 subgroups based on extent of neurological dysfunction as described in the patients’ medical records. Group one (n = 7) was neurologically normal, group 2 (n = 6) had questionable or mild developmental delay, and group 3 (n = 3) had a documented gross developmental delay or neurological disorder. When groups 2 and 3 were removed from the analyses, and the comparison was made between the neurological normal HI group and the NH group, the results mostly remained the same. The exception was that, although the difference in mean volume for both GM and WM between the NH and HI group are significant (P = 0.001), the expected proportion of incorrectly rejected null hypothesis did not reach statistical significance. However, this is likely because of the small sample size in the HI group (n = 7) as...
Table 2
Volume differences between HI and NH subjects by tissue type

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Mean (mm$^3$)</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI</td>
<td>GM 1307</td>
<td>NH 1168</td>
<td>139</td>
<td>60</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>WM 180</td>
<td>333</td>
<td>-152</td>
<td>61</td>
<td>2.48</td>
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<tr>
<td></td>
<td>Total (G + W)</td>
<td>1487</td>
<td>1500</td>
<td>-13</td>
<td>20</td>
</tr>
</tbody>
</table>

Note: Adjusted means and standard errors (SEs) are reported along with the t value, degrees of freedom (df), and P value for the difference in means (corrected for multiple comparisons). Values are reported in units of mm$^3$.

Table 3
Asymmetry in volume (in mm$^3$) between left and right hemisphere aHG ROI by hearing status

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Mean (mm$^3$)</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI</td>
<td>GM 1526</td>
<td>NH 1275</td>
<td>241</td>
<td>168</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>WM 1745</td>
<td>235</td>
<td>-150</td>
<td>112</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>Total (G + W)</td>
<td>3271</td>
<td>2625</td>
<td>-100</td>
<td>3.03</td>
</tr>
</tbody>
</table>

Note: P values reported have been corrected for multiple comparisons.

Table 4
Asymmetry between Left and Right hemisphere aHG ROI volume (in mm$^3$) by tissue type

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Mean (mm$^3$)</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM</td>
<td>1352</td>
<td>1095</td>
<td>257</td>
<td>66</td>
<td>3.91</td>
</tr>
<tr>
<td>WM</td>
<td>301</td>
<td>242</td>
<td>59</td>
<td>26</td>
<td>2.24</td>
</tr>
<tr>
<td>Total (G + W)</td>
<td>1653</td>
<td>1337</td>
<td>317</td>
<td>49</td>
<td>3.72</td>
</tr>
<tr>
<td>GM/WM ratio</td>
<td>8.0</td>
<td>6.3</td>
<td>1.7</td>
<td>0.33</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Table 5
Asymmetry in volume (in mm$^3$) between left and right hemisphere aHG ROI by hearing status

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Mean (mm$^3$)</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>P</th>
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</tr>
</tbody>
</table>

Note: P values reported have been corrected for multiple comparisons.

indicated by large standard error (GM: SE = 95; WM: SE = 97). This suggests that the primary influence on the GM and WM volumes in aHG is hearing loss rather than neurological status. Since the neurological variations did not seem to have an effect on our measures, only the results of the HI group as a whole will be discussed. Because of the referral pathways and variable evaluations of the NH group, it is not possible to make similar classification of neurologically normal and abnormal subjects among this cohort. Although the MRI scans were read as falling within normal limits, this does not rule out the possibility of neurocognitive problems. Consequently, we are not able to make comparisons of homogenous groups of true neurologically normal children with and without hearing impairment.

Asymmetry results between groups are presented in Table 3. Hemispheric asymmetry analyses of the total volume of aHG revealed a significant L > R asymmetry in NH infants (P = 0.001), but this pattern was nonsignificant in HI infants (P = 0.193). It is worth noting that the left > right asymmetry trend is in the same direction in both groups but the increased variability in the HI group does not allow the differences to reach significance.

When we compared the difference between the left and right aHG by tissue class, regardless of hearing status (Table 4), the difference was statistically significant for GM (P = 0.0008), WM (P = 0.038), and total aHG volume (P = 0.001) with the left aHG having greater volume than the right side. The ratio of GM/WM matched these results with a significantly higher GM to WM ratio in the left aHG (P = 0.0005).

Results of the whole-brain VBM followed a similar trend as the ROI analyses in which the HI group had areas of decreased WM volume and areas of greater GM volume in regions related to auditory function. There were no areas of greater WM in HI infants; however, there were several areas in the frontal lobe, cerebellum, and thalamus showing greater GM in the NH group. Discussion of these areas and areas not directly related to auditory function is beyond the context of this paper. Furthermore, because we do not have a purely neurologically normal control group, it does not seem appropriate to discuss differences in the VBM findings that extend beyond the scope of the auditory system (which we have verified as normal in the control group). Table 5 lists coordinates of regions of significantly increased GM and decreased WM in the HI group. Figure 4 shows areas of GM and WM differences that are significant corresponding to Table 5. HI showed up as an area of greater GM and less WM in the HI group, consistent with aHG ROI results. The 3D insets in Figure 4 visualize the GM and WM differences in HG more clearly and provide an orientation to the exact position of the auditory-related VBM results.

Discussion
This anatomical imaging study and volumetric analysis of aHG in infants with congenital hearing loss suggest that significant changes exist at the macroanatomic level in region of the auditory cortex as a result of auditory deprivation by 1 year of age. This is the first study to find significant changes in aHG of children with hearing impairment so early in their development. The main findings reported here are increased GM and decreased WM in aHG in HI relative to NH infants and a concomitant increase in GM/WM ratio in the HI group. Our hypothesis, that the total volume of aHG would be similar in NH and HI subjects was supported, indicating that aHG has developed to a normal size at 1 year of age despite auditory deprivation. Adult studies have found similar results, attributing this to functional plasticity (Emmorey et al. 2003; Penhune et al. 2003; Shibata 2007). Measures of total volume, however, present an incomplete picture of structural development in the presence of congenital hearing impairment. Estimation of GM and WM volumes separately, using automated segmentation methods within the aHG ROIs, gives a more detailed picture of cortical development in this region under the influence of congenital hearing impairment.

The increased GM volume in aHG observed in HI infants was an unexpected finding and has not been observed in studies with deaf adults. This finding may relate specifically to development in infancy and it suggests an early aberration in the developmental trajectory of GM in HI infants, which may normalize by adulthood, possibly through cross-modal plasticity (Giraud et al. 2001). Abnormalities in GM thickness have been reported in developmental disorders such as autism (Carper et al. 2002; Hardan et al. 2006). In typically developing children, GM density generally declines with age and advancing maturity and is therefore larger when immature (Huttonlocher 1979; Gogtay et al. 2004). Larger GM volumes in HI children may correspond to immature cortex.

Looking further into neurodevelopmental processes, particularly synaptogenesis, in animal models may help explain the greater GM volume in deaf infants. Synapse development is similar in humans and other mammals except that animal brain development generally progresses more rapidly than in humans. During synaptogenesis, there is a rapid formation of synapses which occurs in humans from 2 months before birth to early in
infancy. Synapse elimination or pruning begins after a synaptic peak is reached and continues into childhood (Huttenlocher and Dabholkar 1997; Bourgeois et al. 2000). These events can be influenced by environmental factors and individual experience (Bourgeois et al. 2000). Perinatal and particularly postnatal sound stimulation is critical for normal synaptogenesis of PAC (Kral et al. 2005).

Several findings support delayed maturation of primary cortices in visually and HI animals (Winfield 1981; Kral et al. 2005). Synapses form at a slower rate in PAC and primary visual cortex in deaf and blind cats, respectively (Winfield 1981; Kral et al. 2005). In normal development, the synaptic peak is reached through an overproduction of synapses, which are then pruned or eliminated throughout childhood to reach normal adult levels. Peak synaptic density is achieved in PAC approximately 3 months postnatally in humans (Huttenlocher and Dabholkar 1997). In HI cats, the synaptic peak is not only delayed by about 2 months but is also greater in density than NH cats (Kral et al. 2005). Congenital deafness in humans may have a similar impact on these early developmental processes as reported in deaf animal models.

This evidence suggests that increased GM volume in deaf infants may be the result of delayed synaptic maturation in which delayed synaptogenesis produces a larger peak and pruning is subsequently delayed. Synapses are gradually eliminated throughout childhood, but studies in nonhuman primates show that there is first a period of rapid reduction after the peak is reached (Rakic et al. 1986). In fact, synaptic density fell 17% in normal cats within 40 days of the peak (Winfield 1981). Depending on the importance of sound stimulation in the synaptic pruning process, a disturbance of the normal trajectory for elimination of unused synapses could create a large disparity between the GM volume of HI and NH subjects who are at different developmental stages. Though the exact stage of synaptogenesis in the infant group of this study is unknown since we cannot observe cellular structure, it is feasible that the NH infants have started the pruning processes and may even be past the rapid phase. The HI infants may still be near their

Table 5

<table>
<thead>
<tr>
<th>Location</th>
<th>MNI coordinates</th>
<th>Cluster size (kE)</th>
<th>Z</th>
<th>P_(uncorrected)</th>
<th>P_(FDR-corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM HI&gt;NH</td>
<td>Left inferior frontal</td>
<td>−45 10 14</td>
<td>929</td>
<td>4.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Left mid-temporal</td>
<td>−47 45 25</td>
<td>900</td>
<td>3.72</td>
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<td>Right parietal, angular</td>
<td>40 59 43</td>
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<tr>
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<tr>
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<td>44 47 4</td>
<td>1406</td>
<td>4.29</td>
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</tr>
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<td>12 73 37</td>
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<td>3.70</td>
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<tr>
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<tr>
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<tr>
<td></td>
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<td>313</td>
<td>3.76</td>
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<tr>
<td></td>
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<td>313</td>
<td>3.76</td>
<td>&lt;0.001</td>
</tr>
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</table>

Note: Centroids of differences are reported in the Montreal Neurologic Institute (MNI) coordinates referenced to the CCHMC76 reference frame (Altaeye et al. 2008).

Figure 4. VBM performed in SPM5 shows (A) areas of greater GM in HI infants and (B) areas of greater WM in NH infants. Slices are not equidistant but were chosen to show all significant regions greater than 100 clusters. Images are presented in radiological orientation. The 3D insets provide a visual orientation to the reader for the location of the main GM and WM differences occurring in aHG between the groups.
synaptic peak in PAC. This could account for the difference in GM volume found between NH and HI infants. Interestingly, synapse density in sensory deprived animals eventually reaches normal levels by adulthood. This is consistent with normal GM levels in deaf adults and normal synaptic activity and synaptic density in cat studies (Winfield 1983; Emmorey et al. 2003; Penhune et al. 2003; Kral et al. 2005; Shibata 2007).

This study also found a significant decrease in WM in HI compared with NH subjects, consistent with our hypothesis. This WM deficit is consistent with previous reports in adults, signifying that auditory deprivation causes either abnormal formation of WM or early degeneration in infancy (Emmorey et al. 2003; Shibata 2007). Generally, axons increase in size from 1 to 6 months of age and myelination is most active during the first year of life in humans (de Graaf-Peters and Hadders-Algra 2006). Visual deprivation in cats during this time causes a large decrease in the number of myelinated fibers in visual cortex. This trend is maintained into adulthood, never reaching normal levels (Winfield 1983). Consistent with the results of prior studies, our findings provide further evidence that WM does not develop normally in aHG of deaf individuals, beginning during infancy.

Cortical development studies suggest that the growth trajectories of GM and WM are interrelated. GM pruning with age is influenced by WM proliferation (Sowell et al. 2001, 2003, 2004; Gogtay et al. 2004). Thus, delayed tissue development in HI infants is partly due to the immaturity of the other tissue type. Structure and function are also directly related in that if one is delayed the other is likely delayed as well. Looking at the brain globally, primary sensory areas mature before higher association areas, following functional maturation (Gogtay et al. 2004). More specifically, for example, a longitudinal study found that GM maturation was positively related to vocabulary performance (Sowell et al. 2004). Since the children in this sample have had minimal to no auditory experience, it follows that PAC might not develop normally. The results of this study are consistent with studies of cortical growth, which suggest that GM and WM growth trajectories are interrelated and follow functional development.

In contrast to previous studies, NH and HI infant groups examined here did exhibit differences in left to right asymmetry of GM and WM (Penhune et al. 1996, 2003; Emmorey et al. 2003). Although the pattern is in the same direction for both groups, the HI group does not show a significant L > R asymmetry as seen in the NH group. This decreased left hemisphere specialization in HI infants suggests that auditory input may be required for early asymmetry development. In accordance with previous studies, hemispheric specialization may have functional implications (Harris et al. 2009). For instance, an infant with hearing impairment with a leftward aHG asymmetry may have better performance with a cochlear implant than a HI infant without this asymmetry. With both hearing groups combined, all tissue types demonstrated a leftward asymmetry (GM, WM, total, and G/W ratio) for aHG, which is generally consistent with previous studies of PAC cytoarchitecture and HG volume (Rademacher et al. 2001; Emmorey et al. 2003; Penhune et al. 2003).

The whole-brain VBM analyses revealed GM and WM trends in aHG similar to the ROI-based results and suggest that other areas of the brain that are affected by auditory deprivation and may be part of an auditory processing network. WM differences seem to be more robust with higher corrected significance values. Both this study and Shibata (Shibata 2007) found a similar region of WM deficit in the cerebellum. That report notes that this region has been shown to be active during verbal tasks in functional imaging studies (Gates and Yoon 2005), further supporting the hypothesis that these areas play a role in auditory processing. Other reports also note the potential role of the cerebellum in auditory processing (Huang et al. 1982; Petacchi et al. 2005; Sens and de Almeida 2007).

The primary limitation of this study was the small sample size of the HI group. However, even with the small sample, we were able to see significant differences between groups. The HI cohort was also a heterogeneous group with about half having potential neurological delays or disorders. Our raters were not blinded to hemisphere when drawing ROIs, which may have introduced some bias. Our age span of 12 months was rather broad considering the rapid cortical and neurocognitive development occurring during infancy. Additionally, the difference in age between the NH and HI groups was significant. For these reasons, we controlled for subject age in statistical analyses. Future studies could confirm these results with a larger and more homogeneous cohort to better study age differences in GM in particular.

The structural integrity of aHG may relate to the diversity of outcomes in CI recipients. Although it is unknown whether restored hearing through a cochlear implant can reverse these structural deficits, given that the cochlear implant device itself can be a relative contraindication for MRI. Future research could correlate preimplant WM integrity with hearing and speech performance before and after cochlear implantation. These findings reinforce current trends toward earlier intervention with CI in congenitally deaf infants (Miyamoto et al. 2008).

Results of this study illustrate on a macroanatomic level that a lack of auditory stimulation may interfere with normal cortical GM and WM maturation in primary auditory areas located in aHG. These macroanatomic changes can be combined with other evidence supporting early disruption of normal structural development in congenital deafness. GM, rather than WM, seems to have a better chance of ultimately developing to its potential volume given the results of deaf adult studies. Continued research into the early development of PAC in deaf infants may lead to a better understanding of sensitive periods and ideal cochlear implant age windows.

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Notes
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References


