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Alterations of grey matter asymmetries in adolescents with prelingual deafness: A combined VBM and cortical thickness analysis

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Abstract. *Purpose*: Prelingual deafness has been shown to lead to brain reorganization as demonstrated by functional parameters, but anatomical evidences still remain controversial. The present study investigated hemispheric asymmetry changes in deaf subjects using MRI, hypothesizing auditory-, language- or visual-related regions after early deafness.

Methods: Prelingually deaf adolescents ($n = 16$) and age- and gender-matched normal controls ($n = 16$) were recruited and hemispheric asymmetry was evaluated with voxel-based morphometry (VBM) from MRI combined with analysis of cortical thickness (CTh).

Results: Deaf adolescents showed more rightward asymmetries ($L < R$) of grey matter volume (GMV) in the cerebellum and more leftward CTh asymmetries ($L > R$) in the posterior cingulate gyrus and gyrus rectus. More rightward CTh asymmetries were observed in the precuneus, middle and superior frontal gyri, and middle occipital gyrus. The duration of hearing aid use was correlated with asymmetry of GMV in the cerebellum and CTh in the gyrus rectus. Interestingly, the asymmetry of the auditory cortex was preserved in deaf subjects.

Conclusions: When the brain is deprived of auditory input early in life there are signs of both irreversible morphological asymmetry changes in different brain regions but also signs of reorganization and plasticity which are dependent on hearing aid use, i.e. use-dependent.

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1. Introduction

When auditory input into central auditory system is reduced in subjects with severe sensorineural hearing loss, other sensation inputs, such as visual, tactile, and olfactory stimuli, can activate the auditory cortex (Finney et al., 2001; MacSweeney et al., 2001; Neville et al., 1998; Sadato et al., 2005). This phenomenon, known as "cross-modal" plasticity (for reviews, Bavelier and Neville, 2002; Lomber et al., 2010), is the consequence of massive brain reorganization on the anatomical and/or functional level. To better understand the mechanisms of brain reorganization in early deafness, it is necessary to not only find functional signs of reorganization but also morphological correlates. Previous evidence revealed factors which might lead to brain reorganization, such as the use of sign language (SL) (MacSweeney et al., 2008; Meyer et al., 2007; Sadato et al., 2005), hearing aids (HA) or cochlear implant (Hwang et al., 2006; Kang et al., 2004; Philibert et al., 2002). Moreover, other disabilities suffered by about 30% of the subjects with hearing loss (such as speech recognition, reading ability and visual attention) may result in brain dysorganization and/or reorganization in deaf individuals as well (Aparicio et al., 2007; Chilosi et al., 2010; Dye et al., 2008; MacSweeney et al., 2001, 2002, 2009).

Although functional brain alterations have been well-documented in individuals with hearing loss suggesting functional brain reorganization in auditory-, language-, or visual-related regions (Aparicio et al., 2007; Bosworth and Dobkins, 1999; Capek et al., 2008; Finney et al., 2001; MacSweeney et al., 2001, 2002, 2009; Meyer et al., 2007; Neville et al., 1998; Sadato et al., 2005), investigations of anatomical reorganization either mainly focuses on auditory cortices (Emmorey et al., 2003; Penhune et al., 2003) or show inconsistent results which might be caused by different samples or image analysis techniques (Leporé et al., 2010; Li J et al., 2012; Li Y et al., 2012; Shibata, 2007). For example, Leporé et al. (2010) found changes of the frontal lobe white matter regions including Broca's area and adjacent regions involved in motor control and language production by using tesor-based analysis, and Shibata (2007) reported preservation of grey matter but deficit of the white matter in the posterior superior temporal gyrus by using voxel-based morphometry (VBM). Li Y et al. (2012) used diffusion tensor imaging and tract-based spatial statistics, and revealed reductions of FA values in bilateral superior temporal cortex and the splenium of corpus callosum in deaf subjects. Besides, our previous study (Li J et al., 2012) detected white matter volume reduction in the left middle frontal gyrus and right inferior occipital gyrus in deaf adolescents using VBM analysis. In addition, changes of cortical thickness were found in the left precentral gyrus, right postcentral gyrus, left superior occipital gyrus and left fusiform gyrus in deaf adolescents. Therefore, further studies are needed that target the anatomical reorganization in prelingually deaf subjects which may be important to understand underlying mechanisms of brain plasticity.

One gross anatomical measure is the well-known hemispheric asymmetry, a feature of normal human brains which is known to relate to hemisphere-specific functional specializations. Hemispheric asymmetries may be of hereditary, developmental, sexual and pathological origin (for review, Toga and Thompson, 2003). Anatomical asymmetries were detected most frequently in the planum temporale with a robust leftward ($L > R$) asymmetry (Anderson et al., 1999; Eckert et al., 2008; Geschwind and Levitsky, 1968; Good et al., 2001; Wada et al., 1975), as well as in frontal ($L < R$) and occipital ($L > R$) regions (Chiu and Damasio, 1980; LeMay, 1977, 1984). Since asymmetries are inherited and "normal", abnormalities can also come about when either one side is over- or underdeveloped. Thus, asymmetries reflect not only normal brain organization but also may indicate pathological states (impaired function) or "above-normal" states ("hyper-normal" function) in one hemisphere.

Identifying changes associated with brain asymmetries has become popular in the neurosciences where asymmetry measures are often related to different functional states. The underlying assumption is that anatomical alterations of brain asymmetries relate to functional pathology, training or over-use. Studies with healthy individuals revealed functional dominance of the left hemisphere for language (Branch et al., 1964; Lehericy et al., 2000; Sommer et al., 2008) and of

the right hemisphere for visual perception (Bryden, 1973; Kimura, 1966). Examples of pathology associated asymmetries are schizophrenics who show altered asymmetries in grey matter (GM) (Kawasaki et al., 2008) and cortical thickness (CTh) (Hamilton et al., 2007), and developmental dyslexia is associated with asymmetries in the language-related planum temporale (Larsen et al., 1990). An example of a "hyper-normal" function is the association of absolute pitch in professional musicians with a more leftward asymmetry in planum temporale (for review, Jäncke, 2009; Luders et al., 2004). Besides, Bosworth and Dobkins (1999) reported a strong right visual field/left hemisphere advantage for motion processing in deaf signers, and this might be due to auditory deprivation or experience with SL. In view of the fact that functional use (or non-use) may be associated with asymmetries in the brains' gross morphology, it is reasonable to hypothesize that alterations of structural asymmetries would be detected in prelingually deaf subjects which are proficient in the use of SL. We believe that morphological asymmetry might comprise a useful marker for brain dysorganization and/or reorganization in individuals with early auditory deprivation.

With the development of computerized image analysis methods, especially the automated analysis of CTh throughout the whole brain (Fischl and Dale, 2000; Lerch and Evans, 2005; Miller et al., 2000), brain asymmetries could be identified on the cortical surface. Hemispheric differences in CTh have been reported in temporal, frontal and parietal regions of normal adults (Haller et al., 2009; Hamilton et al., 2007; Luders et al., 2006), which may provide further insight into hemispheric asymmetries in brain anatomy and reveal the relation to functional asymmetries. Nevertheless, alterations of CTh asymmetries in prelingually deaf subjects have not been investigated.

VBM and CTh analyses have been simultaneously employed to investigate structural abnormalities in autism (Hyde et al., 2010), schizophrenia (Narr et al., 2005) and major depressive disorders (Koolschijn et al., 2010), as well as in musicians (Bermudez et al., 2009) and normal aging (Hutton et al., 2009). While analysis of CTh is specific and constrained to the cortex, VBM can be used to detect differences in sub-cortical GM as well. In addition, since volumetric analysis measures GM volume (GMV) containing mixed information of cortical surface area, CTh, cortical curvature, cortical translocation as well as geometrical information, analysis using the combination of VBM methods and CTh measurements is able to reflect different aspects of GM changes. However, the relationship between CTh and GMV remains to be characterized, and a combination of these two methods has not been performed in brain asymmetry studies.

Based on existing knowledge and our previous study (Li J et al., 2012), we hypothesized structural changes of hemispheric asymmetries would happen in auditory-language- or visual-related regions after early deafness. In the present study, we used optimized VBM with DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) to investigate asymmetrical abnormalities of GMV in adolescents with prelingual deafness. At the same time, we used CTh analysis to evaluate differences of CTh asymmetries between deaf adolescents and normal controls. To reveal the cause of the asymmetrical abnormalities in prelingual deafness, we assessed GMV or CTh within regions where asymmetry changes occurred and compared both groups. To better understand the functional implications of such changes, we correlated biographical parameters, including the severity of hearing loss, age at onset and time duration of using SL and HA, with hemispheric asymmetry patterns of the regions which were found to be altered in deaf subjects. By using a combined analysis of VBM and CTh, we were able to document for the first time anatomical hemispheric asymmetries in deaf adolescents and interpret this as evidence for brain reorganization in the early life of prelingually deaf subjects.

2. Materials and methods

2.1. Subjects

The data used in the present study have been already analyzed in part for our previous study (Li J et al., 2012). A total of 32 right-handed participants were recruited for the study: 16 adolescents with prelingual deafness (age [mean ± SD]: 14.56 ± 2.10 years, range: 10∼18 years, 8 males) and 16 age- ($p = 0.815$) and gender-matched normal controls (age [mean ± SD]: 14.75 ± 2.38 years, range: 10∼18 years, 8 males). All these subjects had normal vision and were free of any other central nervous system (CNS) diseases, psychiatric disorders, significant head trauma or alcohol abuse. All prelingually deaf subjects were recruited from a school for deaf-mutes. The study was approved by the committee at Beijing Tongren Hospital, and

written informed consent was obtained from all the subjects and their parents according to the Declaration of Helsinki prior to their study entry.

2.2. Clinical assessment

All prelingually deaf subjects had severe sensorineural deafness after birth with the better ear having a mean pure tone audiometry (PTA) average air conduction threshold >90 dB of hearing loss and no single frequency better than 45 dB of hearing loss at 500 Hz to 4000 Hz. They were all trained in Chinese sign language (CSL) for at least 4 years (mean ± std: 7.25 ± 2.97 years, 4∼13 years), starting at an early age (mean ± std: 7.09 ± 1.90 years, 3∼10 years). Furthermore, all deaf subjects wore hearing aids with starting age between 1.5 and 10 years (mean ± std: 4.53 ± 2.65 years) and duration of HA use between 5 and 15 years (mean ± std: 10.16 ± 2.76 years). The reason for their deafness was either drug toxicity or inheritance. The effects of drug toxicity on brain regions were excluded because deaf subjects have no symptoms related to CNS disease or psychiatric disorders. Detailed biographical characteristics of our prelingually deaf subjects are shown in Table 1.

2.3. MRI acquisition

High resolution T1-weighted images (3D spoiled gradient echo (SPGR) sequence) were obtained using a 3 Tesla SIGNA whole body MR imaging system (GE Medical Systems, Milwaukee, WI, USA) with an eight-channel phased-array head coil. Scanning parameters were as follows: repetition time (TR) = 9 ms, echo time (TE) = 3.5 ms, inversion time (TI) = 450 ms, slice thickness = 1 mm, flip angle = 13°, matrix size = 256×256, field of view (FOV) = 24×24 cm^2, yielding 196 sagittal slices with in-plane resolution of 0.9375×0.9375 mm^2.

2.4. Data preprocessing

2.4.1. Voxel-based morphometric analysis

Asymmetries of GMV were assessed using the optimized VBM with DARTEL (Ashburner, 2007). The data preprocessing was conducted with Statistical Parametric Mapping (SPM8) software package (http://www.fil.ion.ucl.ac.uk/spm, Wellcome Department of Cognitive Neurology, London, UK, 2008) running on a Matlab 7.9 platform (MathWorks, Natick, MA, USA).

T1-weighted images were first automatically reoriented according to the AC (anterior commissure) – PC (posterior commissure) line in order to improve segmentation accuracy. Then, all these images were partitioned into GM, white matter (WM) and cerebrospinal fluid (CSF) in native space using unified segmentation method (Ashburner and Friston, 2005). The segmented GM and WM were then left-right flipped, and all the flipped and non-flipped images

Table 1
Biographical characteristics of adolescents with prelingual deafness

ID	Age (years)	Gender	Severity of hearing loss (dB)	CSL use (years)		HA Use (years)		Causes of deafness
				Age onset	Duration	Age onset	Duration	
01	13	Female	96.5	8	5	6	7	Inheritance
02	16	Male	118	6	10	6	10	Inheritance
03	18	Male	100	6	12	6	12	Inheritance
04	16	Male	107.5	6	10	2	14	Drug toxicity
05	15	Female	107.5	10	5	10	5	Inheritance
06	13	Female	103.5	9	4	3	10	Drug toxicity
07	10	Male	105	5	7	5	7	Drug toxicity
08	14	Female	110	3	11	1.5	12.5	Drug toxicity
09	16	Female	110	6	10	7	9	Inheritance
10	17	Female	98.5	9	8	9	8	Drug toxicity
11	13	Male	118.5	6.5	6.5	5	8	Drug toxicity
12	17	Male	103	6	11	2	15	Drug toxicity
13	14	Female	112.5	7	7	1.5	12.5	Inheritance
14	12	Male	103.5	8	4	2.5	9.5	Drug toxicity
15	14	Female	119	8	6	3	11	Drug toxicity
16	15	Male	104.5	10	5	3	12	Inheritance

CSL, Chinese sign language; HA, hearing aids.

were aligned using DARTEL algorithm. After alignment, the symmetrical templates were generated with the flipped and non-flipped aligned images from all subjects, including six iterations of average and registration. The procedure began with the generation of an original template computing the average of all the aligned data, followed by the first iteration of the registration on each subject in turn. Thus, a new template was created and the second iteration began. After six iterations, the template was generated, which was the average of the DARTEL registered data. Then, the non-flipped aligned images were normalized to the symmetrical templates, and modulation was performed to correct for volume changes. Since previous processing was in the native space, all the preprocessed images were then transformed to the Montreal Neurological Institute (MNI) space by aligning warped images to MNI152-template. Finally, all these images were smoothed with a 6-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

All the preprocessed GM images were flipped through the mid-sagittal plane (i.e. $x=0$) and the mirrored images were obtained. Asymmetry index (AI) was defined as:

$$AI_{GMV} = 2\,(original\,image - mirrored\,image)\,/\,(original\,image + mirrored\,image) \quad (1)$$

AI images represented hemispherical asymmetries of GMV. Positive voxel values in the left hemisphere indicated the leftward ($L>R$) GMV (lGMV) asymmetries, while the ones in the right hemisphere indicated the rightward ($L<$R) GMV (rGMV) asymmetries.

2.4.2. Cortical thickness analysis

Preprocessing of MR images were conducted by CIVET pipieline (version 1.1.9, http://wiki.bic.mni.mcgill.ca/index.php/CIVET) (Ad-Dab'bagh, 2006; Zijdenbos, 2002). In brief, T1-weighted images were first corrected for intensity non-uniformity using N3 algorithm (Sled et al., 1998). Then, a 9-parameter linear transformation was employed to register all the images to the ICBM 152 template (Collins et al., 1994). The registered images were tissue classified into GM, WM, CSF and background by an artificial neural network classifier (Zijdenbos et al., 1998). The inner (GM/WM interface) and outer (pial) surfaces for each hemisphere were then created using the CLASP algorithm (Kim et al., 2005), and each surface consisted of 40962 vertices and 81920 mesh triangles.

Anatomical correspondence between hemispheres was established based on the Weighted-SPHARM registration (Chung et al., 2007). For each subject, the inner and outer surfaces were first flipped through the mid-sagittal plane and then the Weighted-SPHARM representation for each surface was constructed with the degree $k=78$ and the bandwidth $t=0.0001$. This procedure can be reformulated as heat kernel smoothing, resulting in smooth functional representation of the inner and outer surfaces with the vertex-to-vertex surface correspondence between hemispheres and different subjects which did not need further smoothing. Then, CTh was measured as the Euclidean distance between the corresponding vertex on the inner and outer surfaces, and no additional step of thickness smoothing was required. Similar to the definition of AI for GMV, the AI for CTh at each vertex was defined as:

$$AI_{Thickness} = 2\,(thickness - mirrored\,thickness)\,/\,(thickness + mirrored\,thickness) \quad (2)$$

For each vertex, positive values of AI at each vertex of the left hemisphere represented the leftward ($L>R$) CTh (lCTh) asymmetries, while the ones in the right hemisphere represented the rightward ($L<$R) CTh asymmetries (rCTh).

2.5. Statistical analysis

Voxel-wise analysis was conducted with AI images based on general linear model (GLM) implemented in SPM8. The one-sample t-test was first performed to investigate GMV asymmetries within each group. Then, the two-sample t-test was used to detect abnormal asymmetries of GMV in prelingually deaf subjects relative to normal controls. We fitted the GLM with age and gender as covariates to exclude their effects on brain asymmetries. Statistical parametric maps were thresholded at an FDR-corrected voxel-wise threshold of $p<0.05$, and only the clusters with no less than 30 voxels were reported.

Statistical analysis for CTh asymmetries was performed using SurfStat, a Matlab statistical toolbox developed by Worsley K.J. (http://www.math.mcgill.ca/keth/surfstat) (Worsley et al., 1996, 2004). The AI value was analyzed with a linear model containing age, gender and group as its main effect terms to test the group main effect at each vertex (including

asymmetry patterns within each group and differences between two groups), controlling for age and gender. In the vertex-wise analysis, multiple comparisons were corrected by FDR and significant p threshold was set to 0.05. We only reported the clusters with no less than 30 vertices within it.

To further explore the causes of asymmetrical pattern changes in deaf subjects, absolute values within the regions showing significantly asymmetrical differences were extracted from preprocessed and its mirror images respectively, indicating GMV or CTh from two sides of these regions. The two-sample t-test was then performed to test for group differences of GMV or CTh of bilateral regions, removing the effects of age and gender.

In addition, to learn if the magnitude of morphological hemispheric asymmetries is a function of hearing experience, we calculated Pearson's correlation between AI values within altered regions and biographical parameters (including the severity of hearing loss, age at onset and time duration of using CSL and HA). Positive correlations represented a growing lGMV or lCTh asymmetry with increasing biographical parameters, while negative ones represented a growing rGMV or rCTh. A statistical significance level of $p < 0.05$ was used in correlation analysis and the correlation with $0.05 \leq p < 0.1$ was reported as statistical trends as well.

3. Results

3.1. Voxel-based morphometric analysis

Analysis of brain asymmetry within each group revealed an extensive and consistent pattern of GMV asymmetries in prelingually deaf subjects compared to normal controls (Fig. 1). Statistical T map was superimposed on the MNI template, with significant regions in the left/right hemisphere indicating the leftward/rightward asymmetries. More focal lGMV asymmetries were detected in the temporal lobe, occipital lobe, medial and inferior frontal lobe and medial cerebellum. Brain regions with rGMV asymmetries were mainly located in the posterior and superior frontal lobes, parietal lobe and lateral cerebellum.

Group comparisons between prelingually deaf subjects versus normal controls were performed to quantitatively evaluate significant alterations of GMV asymmetries. The cerebellum (CER) was found to have more rGMV asymmetries in deaf subjects relative to normal controls (Fig. 2 and Table 2). Follow-up analysis revealed the left CER did not significantly differ between groups, and the right CER was found to be significantly larger in deaf subjects (Table 3), which further led to asymmetry changes (Table 4).

Correlation analyses revealed positive and surprisingly high relations between the time duration of HA use and GMV asymmetry alterations in the CER ($r = 0.581$, $p = 0.018$) (Fig. 5A and Table 5).

3.2. Cortical thickness analysis

Similar and extensive asymmetry patterns were observed over healthy and prelingually deaf adolescents (Fig. 3). Significant lCTh asymmetries were mainly located in the superior and middle temporal gyri, inferior and posterior frontal gyri, and occipital lobe, while rCTh asymmetries were detected most in the frontal lobe, including the middle and superior frontal gyri, and in the inferior temporal gyrus and posterior parietal regions.

Group comparisons revealed that the posterior cingulate gyrus (PCG) and gyrus rectus (REG) showed significantly more lCTh asymmetries in prelingualy deaf subjects compared with normal controls (Fig. 4 and Table 2). Moreover, significantly more rCTh asymmetries were found in the precuneus (PCNU), middle frontal gyrus (MFG), superior frontal gyrus (SFG) and middle occipital gyrus (MOG) of prelingually deaf subjects (Fig. 4 and Table 2). Follow-up analysis revealed these asymmetry changes can be explained by either unilateral CTh gain/loss (PCG, PCNU, MFG and MOG) or simultaneous bilateral changes of the structures (REG and SFG) (detailed in Table 3 and 4).

Table 5 depicts the effects of biographical parameters on alterations of CTh asymmetries in prelingually deaf subjects. The leftward ($L > R$) REG asymmetry significantly and negatively correlated with time of HA experience ($r = -0.610$, $p = 0.012$; Fig. 5B). We also observed some statistical trends, that did not reach significance: the average AI value within the PCG showed marginally significant a negative relationship with age at onset of using CSL ($r = -0.425$, $p = 0.099$) and a positive trend was found for duration of CSL use ($r = 0.424$, $p = 0.100$), respectively (Fig. 5C); asymmetries within the PCNU showed a clear trend of positive relationship with age onset of CSL use ($r = 0.469$, $p = 0.067$;

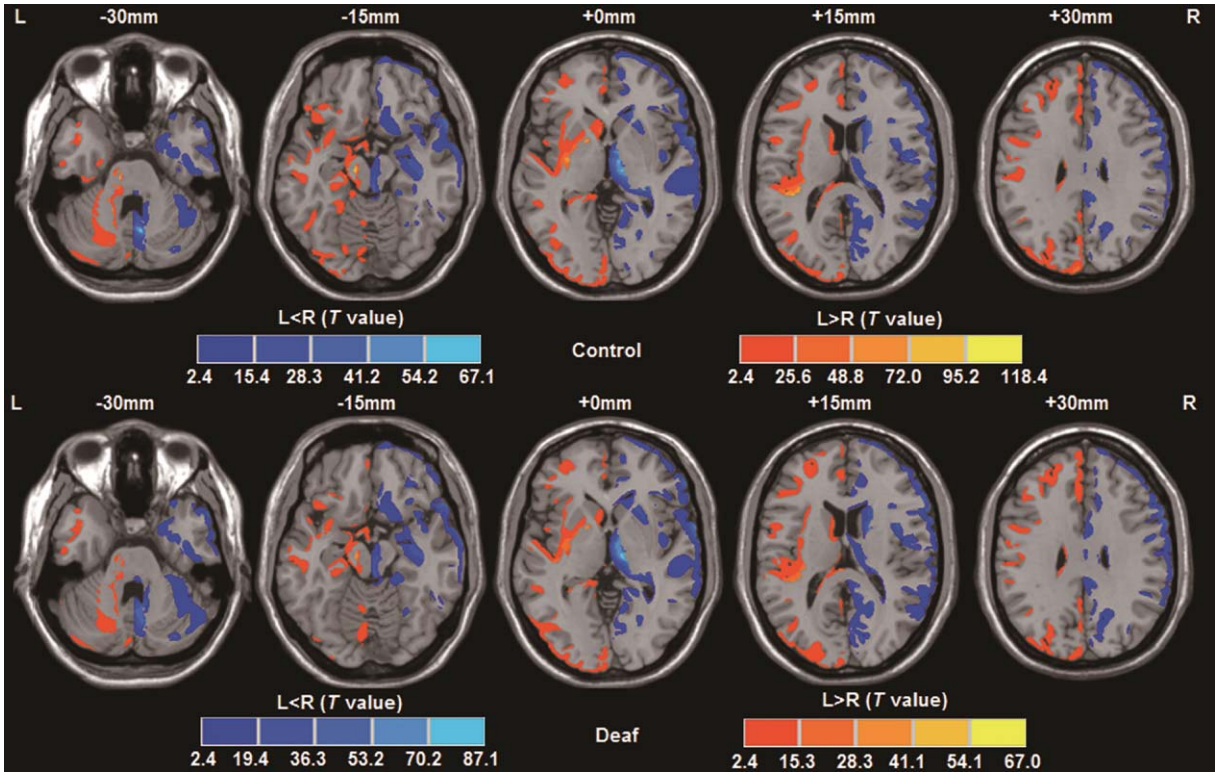

Fig. 1. A multislice display of axial images showing asymmetries of grey matter volume (GMV) in normal controls (top panel) and adolescents with prelingual deafness (bottom panel). The map of T-statistic was superimposed on the MNI template. Multiple comparisons were corrected by FDR, $p < 0.05$, cluster size ≥ 30 voxels. The color bars represented the T values. Significant regions in the left hemisphere indicated the leftward asymmetries ($L > R$, warm color) and the regions in the right hemisphere indicated the rightward asymmetries ($L < R$, cold color). The right hemisphere is on the right side of the image.

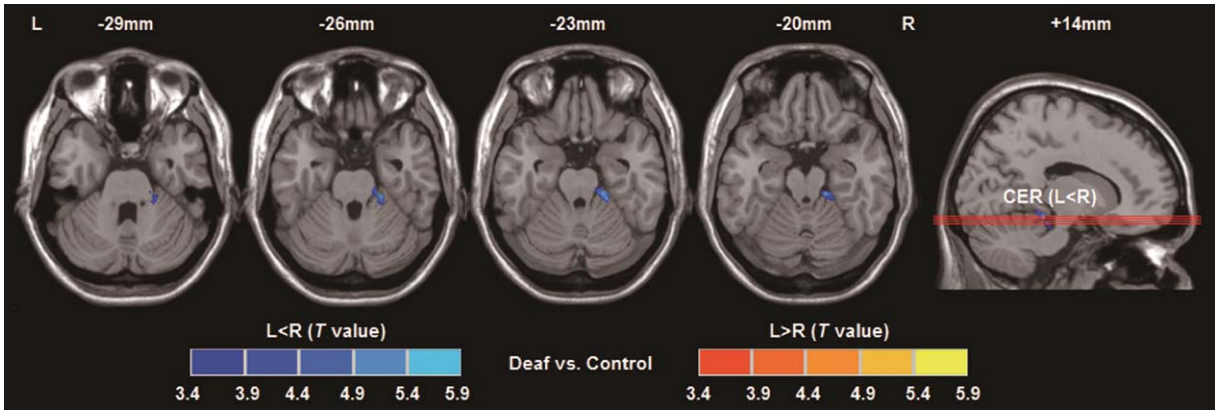

Fig. 2. Brain regions showing significant differences of grey matter volume (GMV) asymmetries between adolescents with prelingual deafness and normal controls. More rightward GMV was found in the cerebellum (CER) of the deaf subjects. The map of T-statistic was superimposed on the MNI template with multislice display of axial images (top). A sagittal slice is also displayed on the right with the red line indicating the location of the axial slices. Multiple comparisons were corrected by FDR, $p < 0.05$, cluster size ≥ 30 voxels. The color bars represented the T values. The significant regions in the left hemisphere indicated the leftward asymmetries ($L > R$, warm color) and the regions in the right hemisphere indicated the rightward asymmetries ($L < R$, cold color). The right hemisphere is on the right side of the image.

Table 2

Brain regions showing significant asymmetry changes of grey matter volume and cortical thickness in prelingually deaf subjects compared with normal controls (FDR corrected for multiple comparisons, $p < 0.05$, cluster size ≥ 30 voxels/vertices)

	Laterality	MNI coordinates			T	p (FDR)	Cluster size	Brain region
		x	y	z				
GMV	L < R	14	–35	–14	5.81	0.047	275	CER
CTh	L > R	–4	–28	31	3.79	0.001	143	PCG
		–5	38	–27	3.71	0.023	82	REG
	L < R	7	–40	62	3.26	0.011	78	PCNU
		38	37	34	3.85	0.017	103	MFG
		16	49	–18	4.12	0.034	99	SFG
		29	–73	39	3.58	0.035	72	MOG

GMV, grey matter volume; CTh, cortical thickness; CER, cerebellum; PCG, posterior cingulate gyrus; REG, gyrus rectus; PCNU, precuneus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MOG, middle occipital gyrus.

Table 3

Characteristics of absolute values of grey matter volume or cortical thickness in bilateral regions with significant alterations in prelingually deaf subjects compared with normal controls

			Control		Deaf		Group differences (p)
			Mean	Std	Mean	Std	
GMV	CER	L	146.484	15.019	147.190	14.517	0.890
		R	133.919	13.939	146.637	14.206	0.017∗
CTh	PCG	L	3.089	0.568	3.786	0.785	0.008∗
		R	3.299	0.420	3.043	0.554	0.142
	REG	L	2.979	0.423	3.360	0.346	0.010∗
		R	3.309	0.435	2.802	0.527	0.006∗
	PCNU	L	2.717	0.228	2.604	0.290	0.247
		R	2.353	0.279	2.906	0.393	<0.001∗
	MFG	L	3.008	0.575	2.348	0.486	0.001∗
		R	2.847	0.475	2.917	0.404	0.638
	SFG	L	3.115	0.521	2.565	0.529	0.006∗
		R	2.631	0.603	3.175	0.494	0.008∗
	MOG	L	3.297	0.341	3.135	0.485	0.287
		R	3.073	0.308	3.603	0.572	0.003∗

Significant group differences are denoted with an asterisk (*$p < 0.05$). GMV, grey matter volume; CTh, cortical thickness; CER, cerebellum; PCG, posterior cingulate gyrus; REG, gyrus rectus; PCNU, precuneus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MOG, middle occipital gyrus.

Table 4

Causes of asymmetry differences in prelingually deaf subjects compared with normal controls

	Brain	Changes over baseline		Asymmetry	Causes of asymmetry changes
	regions	L	R	changes	
GMV	CER	+0.38%	+9.45%*	–9.07%*	gain of the right side
CTh	PCG	+22.56%*	–7.76%	+30.32%*	gain of the left side
	REG	+12.79%*	–15.32%*	+28.11%*	gain of the left and loss of the right side
	PCNU	–4.12%	+23.55%*	–27.67%*	gain of the right side
	MFG	–21.94%*	+2.49%	–24.43%*	loss of the left side
	SFG	–17.66%*	+20.68%*	–38.34%*	loss of the left side and gain of the right side
	MOG	–4.91%	+17.25%*	–22.16%*	gain of the right side

Significant group differences are denoted with an asterisk (*$p < 0.05$). GMV, grey matter volume; CTh, cortical thickness; CER, cerebellum; PCG, posterior cingulate gyrus; REG, gyrus rectus; PCNU, precuneus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MOG, middle occipital gyrus.

Table 5
Effects of biographical parameters on asymmetries of grey matter volume and cortical thickness in the cluster with significant alterations in prelingually deaf subjects

	Brain regions	Severity of		CSL use (years)				HA use (years)			
		Hearing loss (dB)		Age onset		Duration		Age onset		Duration	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
GMV ($L<R$)	CER	–0.319	0.229	–0.145	0.592	0.323	0.222	–0.378	0.149	**0.581**	**0.018***
CTh ($L>R$)	PCG	–0.094	0.728	–0.425	0.099	0.424	0.100	–0.286	0.283	0.398	0.126
	REG	–0.342	0.195	0.157	0.560	–0.399	0.125	0.339	0.199	**–0.610**	**0.012***
CTh ($L<R$)	PCNU	–0.013	0.962	0.469	0.067	–0.087	0.749	0.270	0.313	–0.022	0.937
	MFG	0.269	0.315	0.102	0.707	–0.174	0.519	0.129	0.635	–0.225	0.403
	SFG	0.378	0.148	–0.205	0.447	0.201	0.455	–0.158	0.560	0.208	0.439
	MOG	0.448	0.082	0.201	0.454	–0.275	0.303	0.084	0.757	–0.212	0.430

Significant correlation is represented in bold as * for $p<0.05$; GMV, grey matter volume; CTh, cortical thickness; CSL, Chinese sign language; HA, hearing aids; CER, cerebellum; PCG, posterior cingulate gyrus; REG, gyrus rectus; PCNU, precuneus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; MOG, middle occipital gyrus.

Fig. 5D) and the asymmetry of MOG marginally correlated with the severity of hearing loss ($r=0.448$, $p=0.082$; Fig. 5E).

4. Discussion

We investigated alterations of anatomical brain asymmetries in adolescents with prelingual deafness and provided anatomical evidence of brain reorganization. This was possible by combining VBM and CTh analyses that demonstrated widespread GM changes in hemispheric asymmetries in deaf subjects, which further reflects different aspects of GM changes. More rGMV in the CER was detected by VBM in deaf subjects. CTh analysis revealed more lCTh in the PCG and REG of deaf subjects, while greater rCTh was found in the PCNU, MFG, SFG and MOG. Additionally, correlation analysis revealed that the altered asymmetries in the CER (GMV) and REG (CTh) were significantly affected by time duration of using HA, i.e. auditory experience. Specifically, for the different structures the finding are now described.

4.1. Cerebellum

Previous evidence shows that the CER is involved in motor control as well as cognitive functions, such as learning, attention and language (for reviews, Glickstein, 2007; Jueptner and Weiller, 1998; Middleton and Strick, 1994). We now found that the CER showed significantly more rGMV asymmetries in prelingually deaf subjects due to a gain of volume in the right side. These results are in a good agreement with the findings reported by Leporé et al. (2010) who used tensor-based morphometry to investigate anatomical brain reorganization in prelingual deafness and detected the right CER was bigger in deaf subjects. In addition, a functional study by Aparicio et al. (2007) showed that both the left and right CER (left < right) were activated in deaf group during a lexical decision task, and the right CER was significantly activated in a deaf group during a rhyming task. These results suggested that the CER, especially the right CER, played an important role in phonological processing after deprivation of auditory signals. The functional involvement of the CER in deaf subjects might cause GMV asymmetry alterations in the CER as shown in the present study. Additionally, our correlation analysis showed a significant relationship between CER asymmetries and time duration of using HA. One possible explanation of this HA use effects might be that the right CER was less markedly activated by afferent auditory activation, i.e. the longer the functional use, the smaller the anatomical alteration.

However, our VBM analysis revealed a new result which differed from those of one previous investigation by Shibata (2007). Shibata employed the optimized VBM and found asymmetry patterns of GMV to be preserved in deaf subjects. This discrepancy between their study and our own is probably due to different sample populations used in the studies. Firstly, all the subjects in Shibata's study were adults. In contrast we studied adolescents between 10 and 18 years of age. Secondly, subjects which were fluent in American sign language (ASL) were the focus of the Shibata's study, but all deaf and healthy subjects included in the present study were Chinese. Cultural and environmental differ-

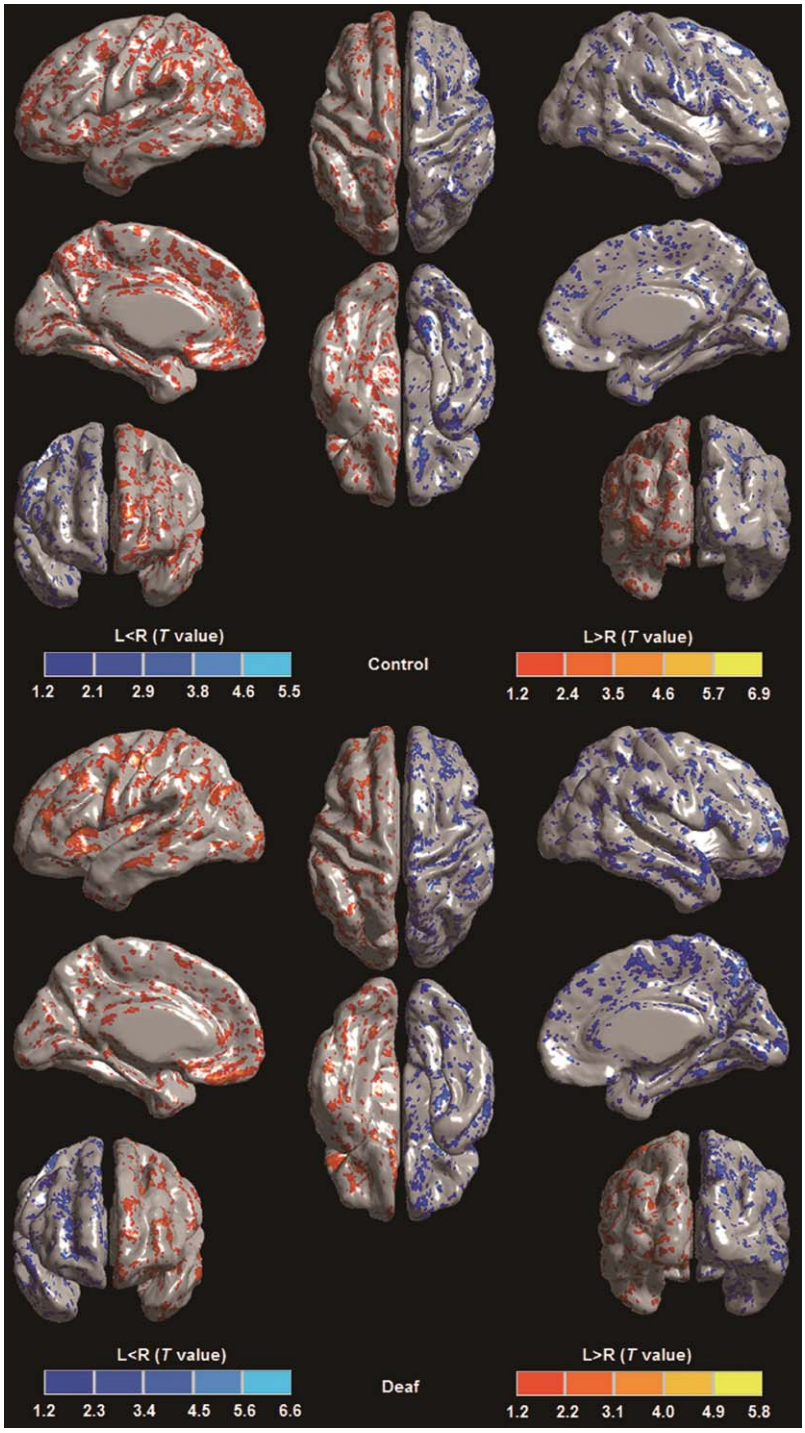

Fig. 3. Corrected *T*-statistic maps showing asymmetry patterns of cortical thickness in normal controls and adolescents with prelingual deafness. The thresholded T map was superimposed on the average middle surface of all the subjects. Multiple comparisons were corrected by FDR with $p < 0.05$, corresponding to an extent threshold of 1.256 for *T*-statistic, cluster size ≥ 30 vertices. The color bars represents the *T* value. Significant regions in the left hemisphere indicated the leftward asymmetries ($L > R$, warm color) and the regions in the right hemisphere indicated the rightward asymmetries ($L < R$, cold color).

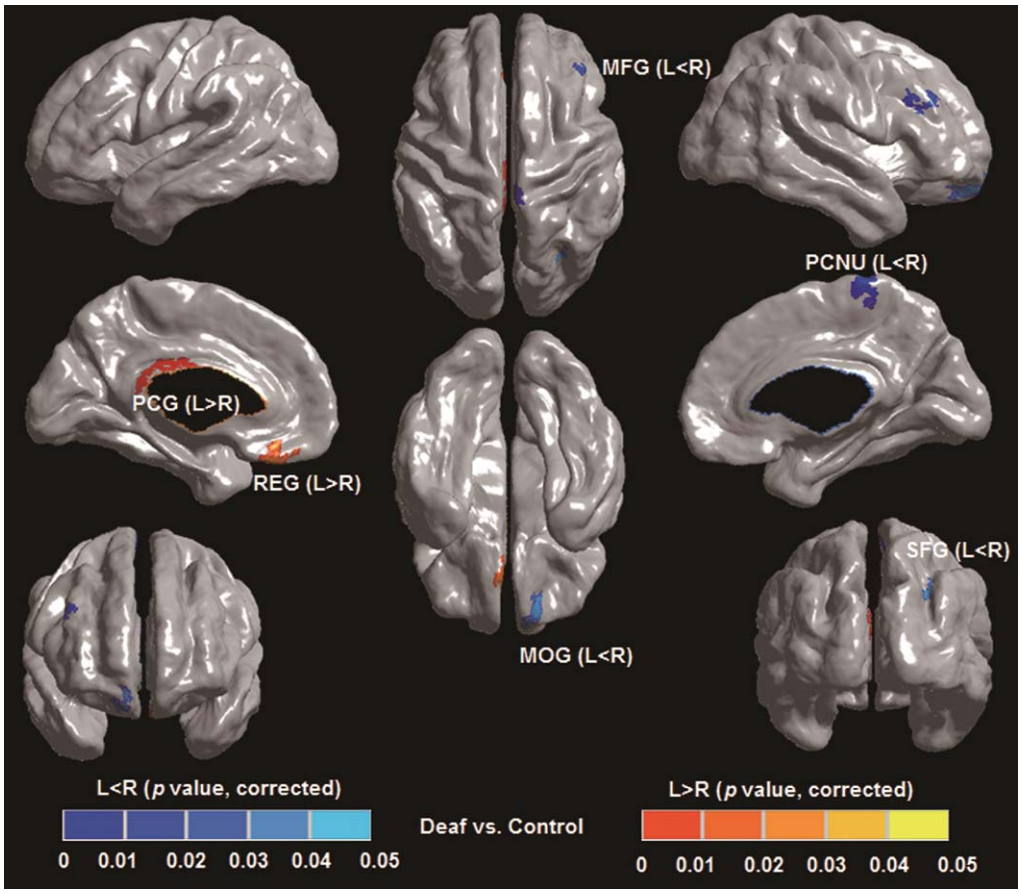

Fig. 4. Regions showing significantly different asymmetries of cortical thickness in prelingually deaf subjects compared with normal controls, superimposed on the average middle surface of all the subjects. The deaf subjects were detected with more leftward CTh in the posterior cingulate gyrus (PCG) and gyrus rectus (REG), and more rightward CTh was found in the precuneus (PCNU), middle and superior frontal gyri (MFG and SFG), and middle occipital gyrus (MOG). Multiple comparisons were corrected by FDR with $p < 0.05$, cluster size ≥ 30 vertices. The color bars represents the statistic p values. Significant regions in the left hemisphere indicated more leftward asymmetries ($L > R$, warm color) in deaf subjects and regions in the right hemisphere indicated more rightward asymmetries ($L < R$, cold color).

ences might explain different vulnerabilities in brain structures (Siok et al., 2004). Thirdly, nine out of sixteen deaf subjects in the present study suffered from deafness caused by drug toxicity, which might be one factor to the variability as well.

4.2. *Posterior cingulated gyrus*

Anatomical changes of the PCG have never been studied in deaf subjects and therefore we are the first to observe anatomical asymmetry alterations of the PCG in prelingual deaf subjects. But the functional roles of the PCG have been reported in deafness before. Kang et al. (2004) suggested that the PCG might play a role in speech learning in deaf children following cochlear implantation (CI); MacSweeney et al. (2002) proposed that PCG is involved in speech reading in profoundly congenitally deaf subjects. Moreover, as reported by Emmorey et al. (2010), the left PCG can be activated by ASL verbs in comparison to fixation in hearing controls, suggesting that the left PCG is related to the use of SL. Interestingly, our study revealed that the PCG showed a significantly greater lCTh asymmetry in deaf subjects due to a significant increased CTh of the left PCG. Therefore, we speculated that the alterations of the asymmetry pattern might be caused by their use of CSL, which was also suggested by our correlation

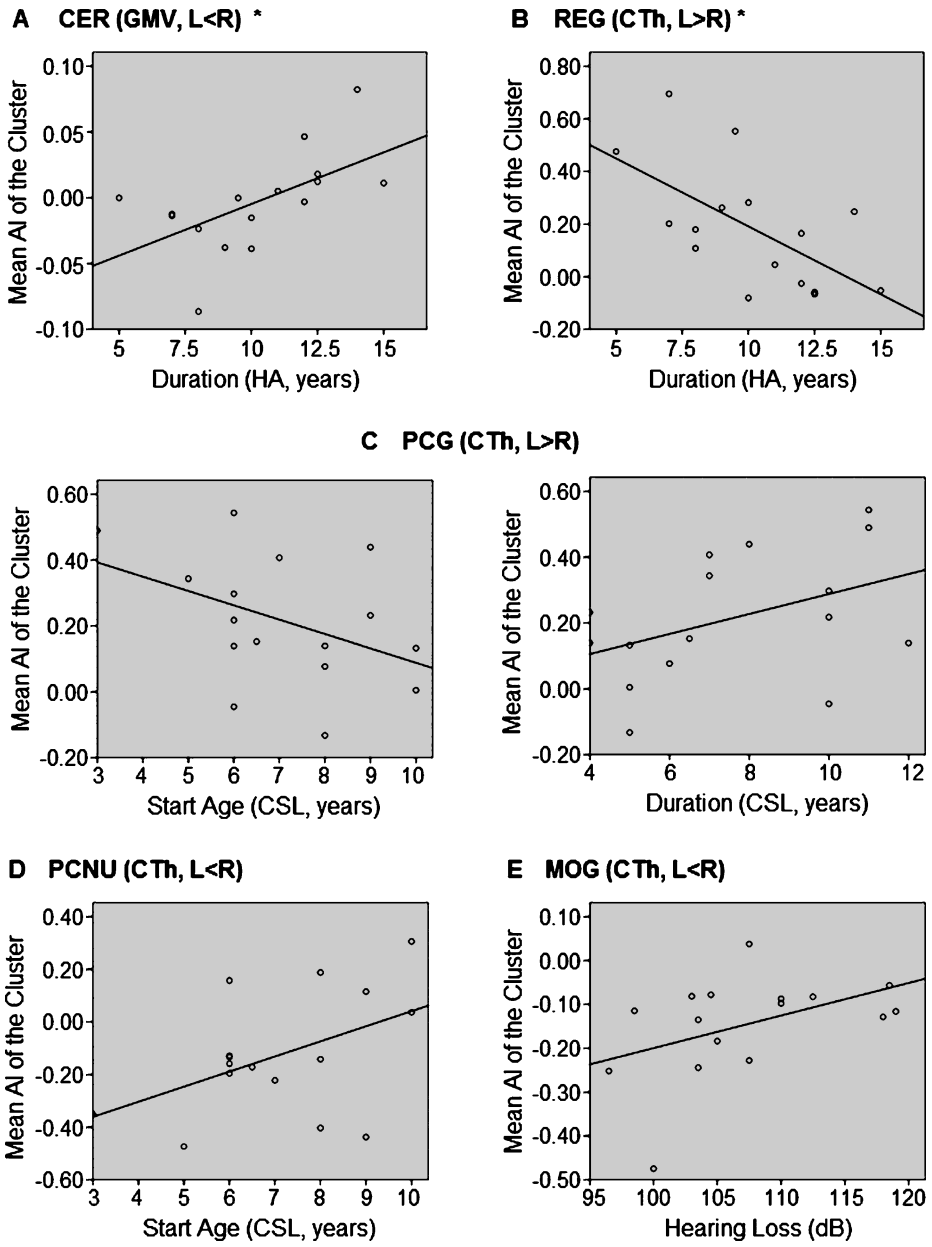

Fig. 5. Effects of biographical parameters (the severity of hearing loss, age onset and time duration of using Chinese sign language (CSL) and hearing aids (HA)) on regions showing significantly altered asymmetries. Only significant ($p < 0.05$) and marginally significant ($0.05 \leq p < 0.1$) effects are presented, including the clusters in (A) the cerebellum (CER), (B) gyrus rectus (REG), (C) posterior cingulate gyrus (PCG), (D) precuneus (PCNU), and (E) middle occipital gyrus (MOG). While positive mean AI values represented the leftward asymmetries, negative values indicated the rightward asymmetries. Significant effects are denoted with an asterisk ($*p < 0.05$).

results showing that the lCTh asymmetry in the PCG had a trend-wise relationship with the time duration of CSL use ($r = 0.424, p = 0.100$). We also found a trend of a correlation between the PCG asymmetry and the age onset of using CSL ($r = –0.425$, $p = 0.099$). This may be taken to suggest that CTh asymmetry alterations in the PCG are related to the brain plasticity before their use of CSL as well, supporting its role in speech reading circuits as suggested by others (MacSweeney et al., 2002; Capek et al., 2008).

4.3. Middle and superior frontal gyri

We found evidence for brain reorganization of the MFG and SFG as indicated by a greater rCTh asymmetry in deaf subjects which has not been reported before. Unlike previous studies, our subjects were Chinese with their native language being non-alphabetic. Chinese characters are notably different from those of alphabetic languages in visual form, semantics, and phonology, and this can cause some differences in neurocognitive mechanisms (Tan et al., 2001; Weber-Fox and Neville, 1996). It has been reported that the left MFG is the main region processing Chinese reading (Siok et al., 2003; Tan et al., 2001) which mediate access to phonology and semantics of Chinese characters (Liu et al., 2006). Deaf subjects have little access to spoken phonology of Chinese words, and less use of the left MFG for phonology processing might cause neural loss in this region, which, in turn, could result in greater morphological loss of CTh in the left MFG. This is in line with Aylward et al. (2003) who observed that the left MFG was less activated in dyslexia children than in normal controls and that bilateral SFG were activated in both normal controls and dyslexic subjects but presented different activation patterns ($L > R$ in normal controls and $L < R$ in dyslexic subjects). Our findings revealed that the asymmetry changes were caused by loss of the left MFG and SFG and a gain of the right SFG of deaf subjects, which seems consistent with these functional evidences. This might explain that inferior reading skills, which were observed frequently in deaf subject, might be associated with asymmetry changes in the MFG and SFG as well.

4.4. Precuneus and middle occipital gyrus

It has been reported that the PCNU and MOG are involved in visuospatial imagery (for review, Cavanna and Trimble, 2006; Renier et al., 2010). Bavelier et al. (2006) have suggested that vision might become more sensitive in deaf subjects due to the deprivation of auditory inputs, resulting in the reorganization of the associated cortical regions. In the present study the PCNU and MOG showed a pattern of greater rCTh asymmetry in prelingually deaf subjects due to thicker CTh on the right side. The right PCNU has been considered as a higher-order area for controlling spatial aspects of motor behavior (Connolly et al., 2000; Grefkes et al., 2004). More recently, Renier et al. (2010) have pointed out that the right MOG was more activated during spatial visual tasks in sighted controls compared to blind subjects, indicating the role of the right MOG in spatial visual processing. In addition, deafness leads to stronger activation in the right MOG during rhyming judgment (Aparicio et al., 2007) and speech reading (Lee et al., 2007). These previous functional MRI investigations are in agreement with our findings of greater rCTh in these two regions, indicating that altered CTh asymmetries in the PCNU and MOG might be due to compensatory effects of visual-related cortices after hearing loss.

4.5. Gyrus rectus

One interesting finding of our study is that a greater lCTh asymmetry in the REG was detected in prelingually deaf subjects; and it was significantly affected by the time duration of HA use. However, the specific function for the REG has not been elucidated. On the one hand, Kang et al. (2004) found the bilateral (more strongly on the right side) REG showed a reduction of glucose metabolism in deaf children with CI, indicating auditory signals had an impact on the REG (especially the right side). This might result in altered CTh asymmetry in the REG and the strong effects of HA use in this region.

4.6. No significant changes in auditory cortices

It is notable that the auditory cortices were preserved in prelingually deaf subjects. One morphometric study by Penhune et al. (2003) performed whole-brain VBM and ROI-based analysis in auditory cortex also found no significant abnormalities in deaf subjects. Emmorey et al. (2003) used manual ROI analysis to explore in-vivo morphometry in auditory brain regions of deaf subjects and found the leftward ($L > R$) asymmetry of the auditory cortex was preserved, although they detected significant differences of WMV but not GMV in the auditory cortices. Lee et al. (2003) used PET to investigate brain metabolism and presented relatively intact metabolism in the auditory cortex in prelingually deaf subjects. Besides, many fMRI studies have revealed the auditory cortex in deaf subjects can be activated by various tasks, such as visual, tactile and olfactory stimuli, indicating that the "cross-modal" plasticity of auditory cortex is a result of auditory deprivation (Finney et al., 2001; MacSweeney et al., 2001; Neville et al., 1998; Sadato et al., 2005). We propose

that neural loss followed by compensatory plasticity might explain the preserved structural asymmetries in the auditory cortex of adolescents with prelingual deafness.

4.7. Methodological issues

The combined analysis of VBM and CTh provides more evidences of brain reorganization in deaf subjects. VBM was used to identify GMV asymmetry changes related to neuronal quantity and size, and CTh was measured to represent another characteristic in GM cortex representing neuronal arrangement in perpendicular direction. GMV contained information of CTh, surface area, curvature, cortical translocation and geometrical information as well. Thus, combining VBM and CTh analyses helps to refine the discovery of GM changes. In line with previous studies (Bermudez et al., 2009; Hyde et al., 2010), our analyses combining VBM and CTh detected inconsistent results: Only one region with altered GMV asymmetry was found in the CER but not in cerebral cortex by VBM, and more cerebral regions, such as PCG, REG, PCNU, MFG, SFG and MOG, showed abnormal CTh asymmetries in deaf subjects. These results revealed by two methods were not contradictory, and the inconsistencies might be further caused by other cortical characteristics. And the abnormalities of GMV and CTh asymmetries we found in our study suggest anatomical reorganizations in adolescents with early auditory deprivation.

Interestingly, the regions detected in our previous study (Li J et al., 2012), which showed thinner CTh in the left precentral gyrus, right postcentral gyrus, left superior occipital gyrus and left fusiform gyrus in deaf adolescents, did not reveal significant changes of brain asymmetry as in the present study. Although not significant, loss of CTh was found on the other side of the detected regions in our previous study (Table 6). Bilateral decreases of the absolute CTh could reduce changes of the asymmetry index in deaf subjects as suggested by Table 6, indicating a different point of view to brain anatomy abnormalities provided by asymmetry analysis.

4.8. Limitations

There are some limitations in the present study. First, the sample size is relatively small, which might result in a reduction of statistical power; hence only trends were found in some analysis so it is necessary to recruit more subjects in future investigations. Second, only volume and CTh are considered in our study, and the follow-up investigations will take into account more cortical characteristics, such as surface area and curvature. Third, the subjects recruited in our study were all adolescents between 10 and 18 years of age whose brains were still under development. Since age and gender were matched between our deaf and healthy subjects, the present study focused on the brain asymmetry alterations between these two groups. Research on age-related changes of brain asymmetries in the present sample are beyond the scope of this paper and will be carried out in our future work.

Table 6
Bilateral cortical thickness changes of the detected regions in our previous study (Li J et al., 2012)

	Brain	Changes over Baseline		Asymmetry
	Regions	L	R	Changes
CTh	PreCG	–16.44%*	–6.42%	–10.02%
	PoCG	–7.69%	–12.70%*	+5.01%
	SOG	–13.31%*	–7.33%	–5.98%
	FFG	–14.95%*	–7.91%	–7.04%

Significant group difference is represented as * for $p < 0.05$; CTh, cortical thickness; PreCG: precentral gyrus; PoCG: postcentral gyrus; SOG: superior occipital gyrus; FFG: fusiform gyrus.

5. Conclusions

In the present study we combined for the first time VBM and CTh analyses and found anatomical alterations of brain asymmetries in different brain structures of adolescents with prelingual deafness relative to normal controls. These asymmetry changes were seen in regions known to be involved in phonological processing, speech reading and visuo-spatial imagery. In contrast, the primary auditory cortex asymmetry pattern did not change. The asymmetry patterns in CER (GMV) and REG (CTh) are a function of duration of hearing-aid use, indicating that the morphological status of these regions is dependent on the restoration of hearing, i.e., it is “use-dependent”. The asymmetry changes in MFG and SFG, in contrast, appear to represent irreversible pathological events. Thus, when the brain is deprived of auditory input early in life there are both signs of irreversible morphological changes in the adolescent brain but also signs of brain reorganization and plasticity which can be induced by hearing aid use.

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