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Age-associated changes of cerebral glucose metabolic activity in both male and female deaf children: parametric analysis using objective volume of interest and voxel-based mapping

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Quantitative analysis of brain activity in the brains of children requires the establishment of age-associated norms. We investigated regional differences in age-associated changes in fluorodeoxyglucose (FDG) uptake in the developmental brains. From 87 (44 male and 43 female) deaf children from the age of 1 to 15, brain FDG positron emission tomography (PET) images were examined after spatial normalization, smoothing, and global normalization to identify brain regions showing a correlation between FDG uptake and age. Using population-based probabilistic volume of interests (VOIs), an objective VOI analysis was performed where normalized relative FDG uptake was measured and their correlations with age were examined in both genders. For the voxel-based analyses, the correlations with age were examined in a general linear model using statistical parametric mapping (SPM99). Both methods revealed that FDG uptake linearly increases with age both in the bilateral inferior prefrontal/orbitofrontal gyri and the right dorsomedial frontal gyrus and decreases in the inferior temporal gyrus and internal capsule white matter. Male children showed age-associated increases of FDG uptake in the right dorsomedial frontal gyrus, and female children in the left dorsolateral prefrontal cortex and thalamus. These changes in FDG uptake in various brain regions may suggest changes in synaptic density or regional activity resulting from normal maturation or deaf-induced adaptation. Caution should be exercised in interpreting the differences in the brain of child patients when compared with adult control's or with a different gender. Further research will be needed to examine if gender difference is manifested in the development rate of behavioral/cognitive functions in association with the age-associated changes of the right medial frontal (male) or the left dorsolateral prefrontal cortices.

Keywords: Development; Metabolism; FDG PET; Deaf children

Introduction

When we want to find abnormalities in brain perfusion or metabolism specific to a disease in children, brain positron emission tomography (PET) or single photon emission computed tomography (SPECT) images are visually interpreted by experts or analyzed in a voxel-wise fashion using statistical parametric mapping (SPM) (Juhasz et al., 2001; Kim et al., 2001, 2002; Vandermeeren et al., 2002; Villemagne et al., 2002). However, developmental changes in terms of brain perfusion or metabolism of children are not well understood because PET or SPECT studies cannot be performed in 'normal' children due to radiation exposure risk. Only volume changes or myelinization patterns have been easily reported (Caviness et al., 1996; Giedd et al., 1996; Kanemura et al., 2003; Mukherjee et al., 2001; Steen et al., 1997).

Instead of relying on reports from brain perfusion or metabolism studies in children, we often have to use adult normal images or images of the probably normal or close-to-normal children as controls for statistical parametric mapping studies (Juengling et al., 2002; Juhasz et al., 2001; Kang et al., 2003; Lee et al., 2002; Vendermeeren et al., 2001; Villemagne et al., 2002). While we know what changes occur during development in children in terms of volumes and displacements of brain structures (Paus et al., 1999; Thompson et al., 2000), we do not know exactly what changes take place in the children's brain in terms of metabolism or perfusion. In rare early reports (Chugani, 1998; Chugani et al., 1987), brain glucose metabolism was found to increase until the age of 2–4 years and then to decrease slowly again to the adult level. Regional differences have been noted but have not been examined in detail (Chugani and Phelps, 1986). The reason is partly due to the poorer resolution of earlier scanners and partly because of the lack of objective means of analytical comparison.

When we use voxel-wise comparison such as statistical parametrical mapping (SPM) method to analyze brain metabolism, brain images are usually normalized in counts and only the relative differences between different regions can be determined. For example, child patients' brain images have been compared on a voxel-to-voxel manner with adult control brains (Juhasz et al.,

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2001; Juengling et al., 2002; Kang et al., 2003; Lee et al., 2002). PET or SPECT images of epileptic (Vendermeeren et al., 2001) or transient ischemic attack patients (Villemagne et al., 2002) have often been used as age-matched disease controls due to lack of normal healthy children control data. It is important to delineate developmental or age-related changes as much as possible even in deaf children since it still could provide valuable information in understanding normal development of brain function.

The brain glucose metabolism of profoundly deaf children has been reported to have prognostic significance for cochlear implant patients (Lee et al., 2001). Younger age and the hypometa-bolism in temporal regions were associated with better outcome following implantation (Oh et al., 2003). There seemed to be a relationship between the age and the glucose metabolism in deaf children. The goal of this study is to examine the developmental metabolic changes in deaf brain to understand the relationship between these two factors. Meanwhile, we would like to know which changes were part of normal development and which were part of deaf-induced changes. Fluorodeoxyglucose (FDG) PET studies are routinely performed on deaf children in our center before cochlear implantation. This is a part of an on-going effort to understand the brain plasticity of deaf children and to evaluate the relationship between the regional brain metabolic activity of deaf patients and the implantation outcome (e.g., speech hearing) (Kang et al., in press). Being interested in examining individual differences in functional brain activity at rest, we became aware of the importance of identifying the time course of regional glucose metabolic activity changes with increasing age during the deve-lopment period, whether or not it is affected by the fact that these children have been deprived of auditory sensory input. Since it has been well known that sex steroid hormones influence brain developments both in function and structure (Cameron, 2001), we also examined if there was a sex difference in the rate of changes in FDG uptake with increasing age during developmental years in these children.

In this study, we examined age-associated changes in FDG uptake using a large size of the deaf children cohort (N = 87). Linear or nonlinear age-associated changes in glucose metabolism in children's brain during developmental years (1–15 years) were studied both with voxel-based analysis and with volume of interests (VOI) analyses using objective and probabilistic VOIs. We modeled a sex difference between a group of male (N = 44) and a group of female (N = 43) children as well as ages in those analyses.

Since it is practically difficult to have PET data from group of normal children, we would not be able to compare the deaf developmental changes with the normal developmental changes.

In summary, the goal of this study is to understand general changes of the brain metabolic activity with increasing ages and sex difference in these changes in the deaf children of developmental ages (from 1 to 15 years old).

Materials and methods

FDG PET was performed on deaf patients as a clinical presurgical evaluation in the Seoul National University Hospital. Informed consent was obtained from the parents or guardians after explaining the procedure, risk, and purpose/benefit of the FDG PET study, which was performed as a preoperative evaluation to predict postsurgical outcome. A total of 87 children with early onset deaf were included. Early deaf are those who were born deaf or became deaf early in life (before or around the time of language acquisition). These patients were the profound deaf without other apparent neurological/psychiatric symptoms (Table 1).

PET images were acquired using an ECAT Exact PET scanner (CTI-Siemens, Knoxville, USA). The axial and in-plane resolutions were 4.3 and 6.1 mm, respectively. Before radiotracer injection, a transmission scan was performed using a Ge-68 rod source to yield the attenuation maps. About 30–40 min after the intravenous administration of 370 MBq of F-18-FDG, 47 slices of the brain emission images were acquired over a 20-min period. Emission images were reconstructed in a 128 × 128 × 47 matrix with a pixel size of 2.1 × 2.1 × 3.4 mm using a filtered back projection method with a Shepp filter having a cutoff value of 0.35 cycles/pixel. All reconstructed images were corrected for attenuation and transaxial images were realigned to yield sagittal and coronal images.

Spatial pre-processing and statistical analysis were performed using SPM99 (Institute of Neurology, University College of London, UK) implanted in Matlab 5.3 (Mathworks, MA, USA). Once converted to Analyze format, the PET images were spatially normalized to an MNI template using SPM99. For global normalization, voxel counts of PET images were normalized so as that mean count of FDG uptake in whole gray matter in each PET image would be 50. These images once globally normalized were subjected to both voxel-based analysis and VOI analysis. Absolute difference or changes in global FDG uptake were not measured or modeled in this study. For the voxel-based analysis, the globally normalized image was smoothed (FWHM 16 mm) with SPM99 before the analysis.

Unlike a previous study with deaf children (Kang et al., in press), we did not attempt to use a study specific template for spatial normalization in this study to make the coordinates of the results comparable with others. Voxel counts of PET images were normalized so that the mean count of FDG uptake in whole gray matter in each PET image would be 50. The counts from spatially

Table 1
Summary of deaf pediatric patients profiles

Group	N	Mean age (SD)	Age range	Deaf onset	Etiology	Age distribution	N
Deaf children	87	5.18 (3.42)[a]	1–15	early	unknown = 42	1 – 2 years old	9
Female	43	5.60 (3.46)	1–15		congenital = 31	2 – 4	26
Male	44	4.77 (3.37)	1–13		meningitis = 12	4 – 6	19
					accident = 1	6 – 8	12
					chicken pox = 1	8 – 10	8
					mumps = 1	10 – 12	8
						12 – 14	4
						14 – 15	1

[a] Duration was approximated as age for early onset (congenital or unknown).

normalized PET images were multiplied by the probability from 92 VOIs and the probability-weighted counts were obtained objectively for all volumes of interest (VOI) (Kang et al., 2001). The 98 VOIs included 88 selected VOIs of the Statistical Probabilistic Anatomical Map (SPAM) of the ICBM (International Consortium for Brain Mapping) and 4 VOIs from primary auditory cortex in both hemispheres, V1, and V2.

For VOI analysis, probability-weighted counts were related to age using linear regression methods. The correlation between the FDG uptake and age was presumed to be linear but a second-order polynomial regression was also examined additionally (StatView, SAS Institute). Considering multiple comparisons, only the areas showing P value less than 0.0005 were presented. Sex difference was also examined in this analysis by using an ANOVA where age, gender, and an interaction between age and gender were modeled. For main effect of gender or age, the same statistical threshold ($P < 0.0005$) was used. However, for interaction between gender and age, a lenient threshold ($P < 0.05$) was used. Nonlinear relationship between FDG uptake and age was studied using the second-order polynomial regression analysis where an F test was performed ($P < 0.0005$) on each VOI region. Only the brain regions that showed significant coefficient for the second-order polynomial regression are reported here.

For voxel-based analysis, the preprocessed PET images were tested with a general linear model with gender as group factor (male group $N = 44$; female group $N = 43$) and age as a covariate for the deaf children. Correlation between FDG uptake and age was presumed to be linear, and both positive and negative correlations were examined. Reported here are the local maxima of clusters which were composed of more than 10 contiguous significant voxels ($P < 0.0005$ uncorrected at voxel level, $T = 3.41$, extent threshold $k = 10$) for the regions which showed linear correlation between age and FDG uptake. The difference was also compared between two groups regar-ding the linear changes. A separate analysis was performed to find the sex difference in brain regional FDG uptake.

In reporting the results of this study, the MNI coordinates of the SPM results were converted into Talairach (Talairach and Tournoux, 1988) coordinate system using a software written by Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

Results

Objective VOI analysis results

Of the 98 regions of interests, five gray matter regions showed linear relation between FDG uptake and age (Table 2). Inferior frontal gyrus both in left (Fig. 1A) and right hemisphere and right medial frontal region were found to be positively correlated with age.

Counts of right inferior temporal gyrus (Fig. 1B) and bilateral parahippocampal gyri were negatively correlated with age. Five white matter regions in both hemispheres showed linear relations with age, including corpus callosum, left anterior limb of internal capsule, and bilateral parietal and bilateral temporal lobe white matter regions.

Significant second-order polynomial regressions were found between ages and the mean FDG uptake in the VOIs in the left putamen [$F(2,84) = 9.87$, $P < 0.0002$; first-order coefficient = −1.48, second-order coefficient = 0.10, $R^2 = 0.190$] (Fig. 1C) and the left anterior limb of internal capsule [$F(2,84) = 25.61$, $P < 0.0001$; first-order coefficient = −1.67; second-order coefficient = 0 09; $R^2 = 0.379$]. The regression curves showed the lowest FDG uptake occurring around age 6–8 years old.

Table 2
Areas showing age-associated linear changes of FDG uptake by population-based probabilistic atlas VOI analysis

Areas	Coefficient	R^2
Left inferior frontal gyrus	0.307	0.157
Right inferior frontal gyrus	0.311	0.161
Right medial frontal gyrus	0.288	0.144
Male ($N = 44$)	0.463	0.322
Female ($N = 43$)	0.095	0.019
Left anterior limb of internal capsule	− 0.456	0.253
Left parahippocampus	− 0.281	0.154
Right parahippocampus	− 0.292	0.178
Right inferior temporal gyrus	− 0.279	0.157
Corpus callosum	− 0.478	0.172
Left parietal lobe white matter	− 0.341	0.304
Right parietal lobe white matter	− 0.341	0.313
Left temporal lobe white matter	− 0.255	0.195
Right temporal lobe white matter	− 0.323	0.263

No region showed significant ($P < 0.0005$) gender effect. However, the right dorsomedial frontal region was the only brain region which showed significant interaction between age and gender [$F(1,83) = 6.188$, $P < 0.02$]. According to regression analysis, significant positive correlation was found in the male ($T = 4.462$, $P < 0.0001$) but not in the female deaf children ($T = 0.897$, $P > 0.30$).

Voxel-based analysis results

A linear relationship was examined between the FDG counts and age on voxel-based SPM analysis including both groups of children. Various brain regions showed significant positive correlations (Table 3) when both the male and the female groups were combined in the analysis. Orbitofrontal, inferior prefrontal, and dorsolateral prefrontal regions in both hemispheres and dorsomedial frontal gyrus in the right hemisphere showed a positive correlation. Bilateral mediodorsal thalamic nuclei and left cerebral cortex also showed the positive correlation.

Negative correlation was found in several gray matter regions including bilateral inferior temporal regions (Tal $x, y, z = 44, -29, -27$: $T = 6.98$ for the right; Tal $x, y, z = -22, -27, -29$: $T = 5.57$ for the left), right fusiform (Tal $x, y, z = 22, -55, -7$: $T = 4.60$), and left inferior parietal region (Tal $x, y, z = 40, -43, 24$: $T = 4.67$). Parahippocampal regions were also included in these gray matter regions. Ventral region of the posterior central gyrus (Tal $x, y, z = -63, -9, 21$: $T = 4.45$) and right occipital pole (Tal $x, y, z = 20, -92, 23$: $T = 4.45$) also showed significant FDG uptake decrease.

FDG uptake decrease was found in extensive white matter regions including the anterior limb of internal capsule (Tal $x, y, z = 28, 3, 16$: $T = 8.46$ for the right; $x, y, z = -24, 8, 14$: $T = 7.55$ for the left), optic radiation (Tal $x, y, z = -30, -66, 9$: $T = 5.25$ for the left; Tal $x, y, z = 26, -65, 12$: $T = 5.07$ for the right), and posterior corpus callosum (Tal $x, y, z = -16, -50, 17$: $T = 4.53$; Tal $x, y, z = 22, -48, 13$: $T = 4.77$) bilaterally.

As sex as a group factor, the brain regions showing age-associated increases in glucose metabolic activity were examined within each group. First, both groups showed the positive corre-

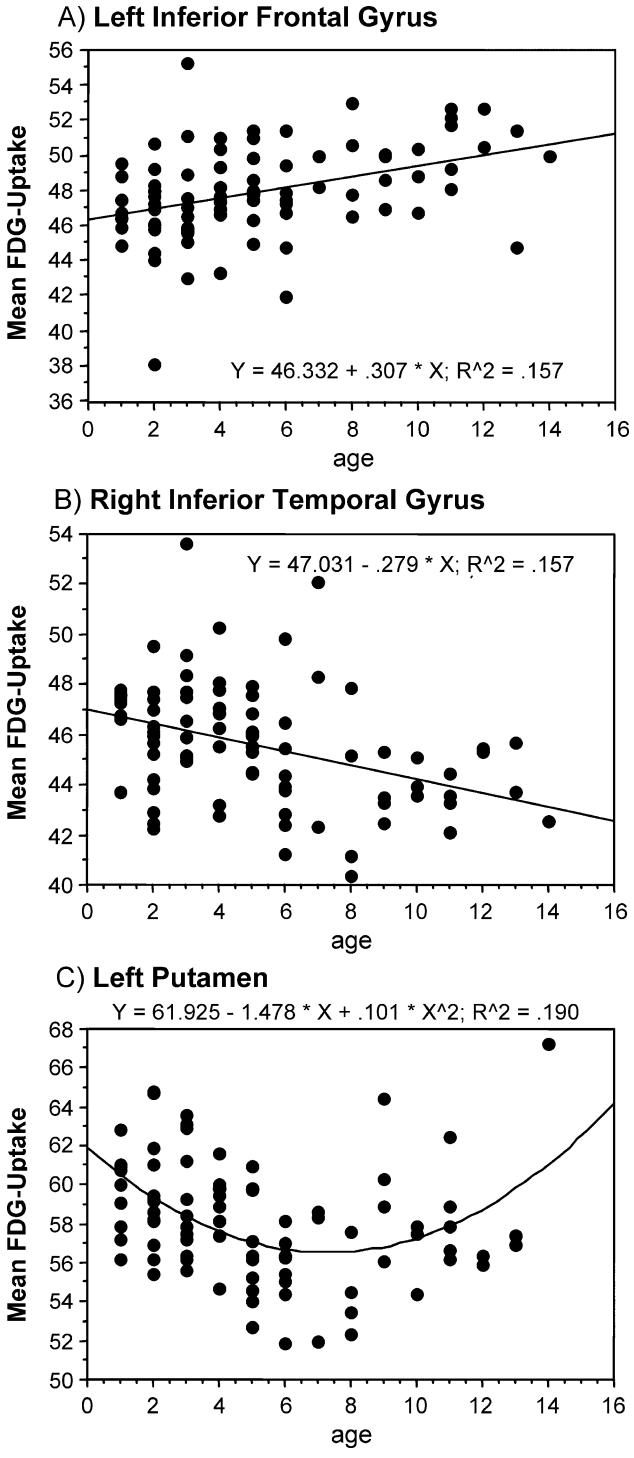

Fig. 1. Regression plots between FDG uptake and age in all deaf children according to VOI analyses. Normalized FDG uptake of the left inferior frontal gyrus (A) showed positive correlation while right inferior temporal gyrus (B) showed negative correlation with age. Left putamen (C) was one of the brain regions showing second-order polynomial correlation with age.

lation in the bilateral orbiofrontal regions (Fig. 2A). Second, the age-associated FDG uptake in the right dorsomedial frontal region (Fig. 2B) was significant only in the male group. Lastly, the female group showed positive correlation in diverse brain regions, such as the left dorsolateral prefrontal cortex (Fig. 2C), the bilateral mediodorsal thalamic nuclei, and the left cerebellar cortex. Decrease of FDG uptake with increasing age was found in extensive white matter regions. The females showed this decrease in greater extent in distribution than the male children given the statistical threshold ($P < 0.0005$ uncorrected, $T = 3.41$). The brain regions showing age-associated increases (Table 4) and decreases (Table 5) in the glucose metabolic activity in each gender are summarized also in Figs. 3A and B, respectively.

Significant group difference in this linear change was not found. Only with a slightly lenient threshold ($P < 0.005$ uncorrected at voxel level, $T = 2.64$), small regions in the right occipital pole (Tal $x, y, z = 10, -95, 3$; $P = 0.004$, $T = 2.75$) and in the right dorsal insula (Tal $x, y, z = 40, -3, 15$; $P = 0.003$, $T = 2.84$) showed the group difference. The former region showed a greater correlation in the female than the male group whereas the latter did so in the male than the female group.

According to a separate analysis comparing group difference only (without considering age factor), the female children in general showed significantly ($P < 0.0005$, $T = 3.41$) greater FDG uptake in the left medial geniculate region (Tal $x, y, z = -18, -29, -4$) (Fig. 4) and in the occipital regions in both hemispheres (Tal $x, y, z = 28, -85, 3$ in the right; $-32, -83, 1$ in the left) relative to the male group. No region of brain in the male children showed greater FDG uptake than that of the female.

Discussion

Our findings reveal that some areas show increased FDG uptake during developmental ageing in deaf children using two different objective methods, namely, objective VOI analysis and voxel-based analysis. Both analyses suggested that relative FDG uptake in the inferior frontal gyri in both hemispheres and in the right dorsomedial frontal gyrus increased as the children got older. Additional analyses modeling sex difference revealed that the age-associated changes in the right dorsomedial frontal region came mostly from the male children. With voxel-based analyses using SPM99, the develop-

Table 3
Areas with age-associated increase of FDG uptake in all deaf children: voxel-based SPM analysis

Regions	L/R	BA	Talairach[a]			T	Cluster size[b]
			x	y	z		
Orbitofrontal gyrus	R	11	36	36	−17	5.91	1007
Orbitofrontal gyrus	L	11	−16	42	−22	5.64	709
Inferior PFC	L	47	−44	38	−12	4.08	
			−46	17	−1	3.98	
Dorsolateral PFC	L	6	−40	10	46	4.77	168
Mediodorsal thalamus	B		2	−19	3	4.58	34
Inferior PFC	R	44	50	11	31	4.36	686
Dorsolateral PFC	R	6	48	8	46	4.16	
Dorsomedial frontal gyrus	R	8/6	4	18	54	4.10	845
Cerebellum	L		−38	−66	−39	3.73	24
Inferior PFC	R	47	50	19	−1	3.57	20

BA, Brodmann's area; PFC, prefrontal cortex; WM, white matter; L, left; R, right; B, bilateral.
[a] Local maxima of clusters composed of more than 10 significant (uncorrected $P < 0.0005$, $T = 3.41$) voxels.
[b] Number of significant voxels (2 × 2 × 2 mm).

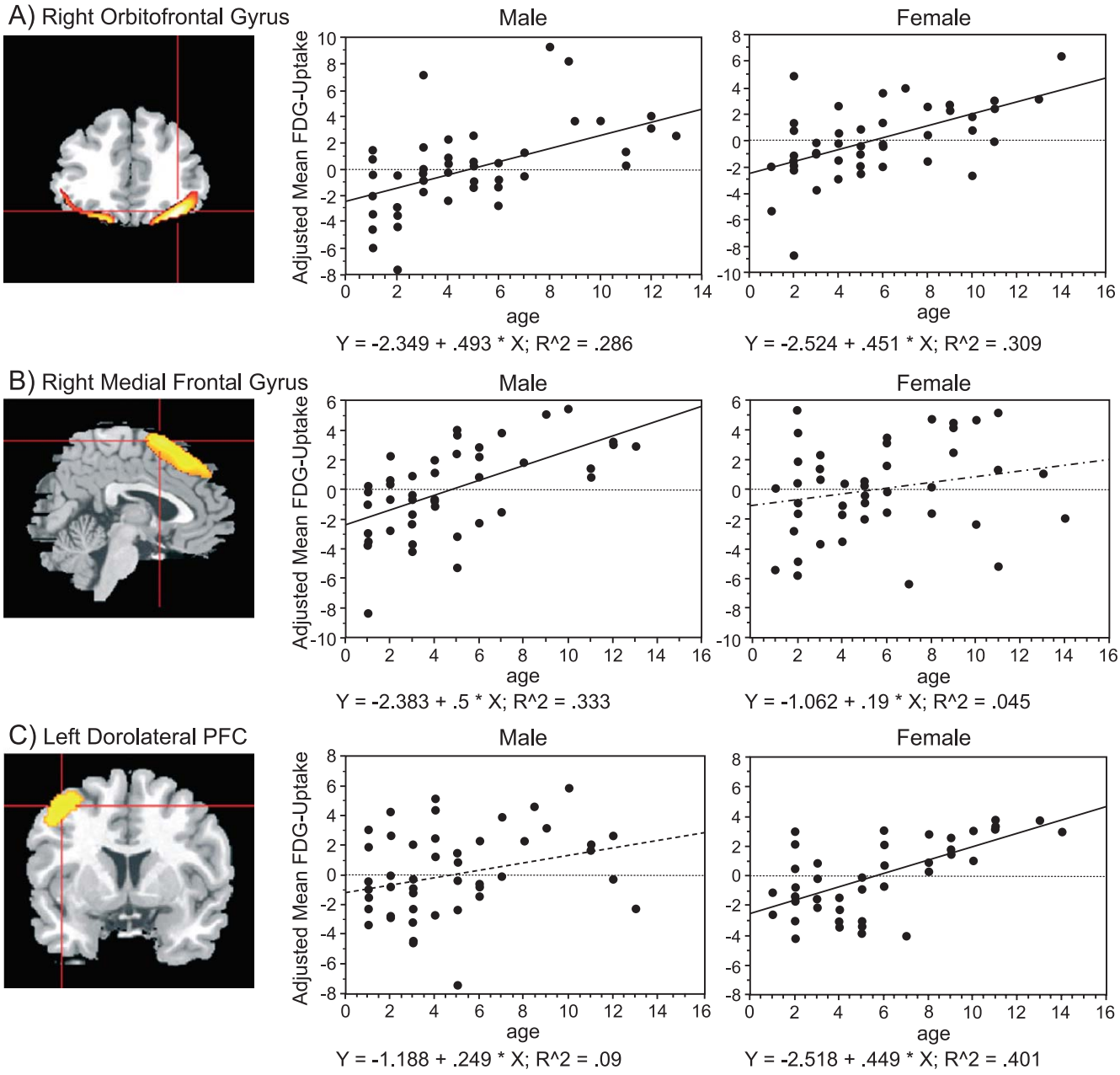

Fig. 2. Brain regions showing significant ($P < 0.0005$ uncorrected) age-related changes depending on the gender. Significant linear increases of FDG uptake were distinctive in the bilateral orbitofrontal regions (A) in both groups. However, the right medial frontal gyrus (Tal $x, y, z = 4, 11, 60$) (B) was only significant in the male group and the left dorsolateral prefrontal region (Tal $x, y, z = -40, 8, 47$) (C) was in the female group only.

mental changes in more restricted brain regions were detected, including bilateral orbitofrontal and dorsolateral prefrontal cortices, mediodorsal thalamus, and cerebellum as well. When the sex difference was considered, the female group showed a strong positive correlation between age and FDG uptake in the left dorsolateral prefrontal region (BA 6), while the male group did so in the right dorsomedial frontal region (BA 6/8/9). Decreased FDG uptake was observed in the right inferior temporal regions in both analyses, while bilateral parahippocampal regions was detected only in the VOI analysis and the left inferior temporal, the right fusiform, and the left parietal region were in the voxel-based analysis. We also observed decreased FDG uptake in many white matter regions including the anterior limb of internal capsule, optic radiation, and corpus callosum (VOI analysis only). They were probably observed in association with progressive myelination of those white matter regions with maturation. However, interestingly, we found this decrease of FDG uptake occurring far extensively in the brain of female children than male children. In general, the statistical threshold ($P < 0.0005$) for VOI analysis was equivalent to the corrected $P < 0.05$ for multiple comparisons while the one adapted for the voxel-based analysis was uncorrected $P < 0.0005$. Therefore, we observed more brain regions in the voxel-based analysis.

These increases and decreases in FDG uptake during growth may be pertinent only to deaf children. As we do not have data from 'normal' children, we might consider several possibilities in interpreting the deaf children data.

Table 4
Areas with age-associated increases of FDG uptake in each gender

Regions	L/R	BA	Talairach[a]			T	Cluster size[b]
			x	y	z		
Male							
Orbitofrontal gyrus	R	11	36	40	−15	4.41	515
Dorsomedial frontal gyrus	R	6	4	11	60	4.01	950
		8	4	29	45	3.89	
		9	2	45	36	3.72	
Orbitofrontal gyrus	L		−16	42	−22	4.00	55
Female							
Dorsolateral PFC	L	6	−40	8	47	4.30	470
Orbitofrontal gyrus	R	11/47	34	34	−20	4.28	209
Orbitofrontal gyrus	L	11	−18	40	−22	4.13	55
Cerebellum	L		−40	−64	−39	4.12	78
Mediodorsal thalamus	B		6	−19	3	3.95	170
Inferior PFC	L	44	−50	14	1	3.65	31
Inferior PFC	L	47	−44	36	−12	3.65	40

BA, Brodmann's area; PFC, prefrontal cortex; L, left; R, right.
[a] Local maxima of clusters composed of more than 10 significant (uncorrected $P < 0.0005$, $T = 3.41$) voxels.
[b] Number of significant voxels (2 × 2 × 2 mm).

Firstly, normal children population can still be represented by these deaf children whose developmental course would be shared by normal children. However, it is known that the brain glucose metabolism is altered in deaf subjects as well as in epilepsy patients or in subjects with neurologically minor episodes (Vandermeeren et al., 2002; Villemagne et al., 2002). Thus, it is difficult to generalize the age-associated changes in this study. Secondly, our findings may reflect biological processes in the developmental brain of deaf people as they adapt to the sound-deprived environment, including lack of experience of auditory language perception and production (Kang et al., 2003). The third possibility is a combination of the above two. We do not have the means to differentiate between these three possibilities, and delineating which brain areas might be relevant to which hypothesis is beyond our reach.

If we adopt the second hypothesis, we can use our findings to explain the developmental changes in the brains of deaf children. Increased brain activity with ageing observed in inferior frontal gyri/orbitofrontal gyri might indicate age-associated developments without auditory sensation. This was in contrast to the fact that no significant age-associated changes were found in the primary auditory regions (A1) or the early visual regions (V1/V2) in either method. Considering that the age is equivalent to the duration of deaf in all deaf children (i.e., early onset deaf), the effect of adaptation will increase with ageing. These age-associated changes in FDG uptake might represent brain adaptation to abnormal sensory environment over time. Another possibility for the age-associated increase in these regions is lack of pruning after supernumerary synaptic generation in the normal early development (Chechik et al., 1999; Deggouj et al., 1995; Seeman, 1999). Lack of environmental auditory input might make pruning less efficient and concomitant FDG uptake higher than the adjacent normal areas. Decreased activity with ageing in several gray matter regions such as inferior temporal gyri, fusiform, or parietal region might be caused by the less use of somatosensory and higher multisensory areas in everyday life. These areas of deaf children might have become more and more efficient in sensory-motor system with ageing and FDG uptake shall also decrease.

Chugani et al. (1987) reported earlier that brain glucose metabolism in the children with epilepsy increases until the age of 2 years and reaches a plateau at about age 4. The metabolic rates then decreased slowly to the adult level until 20 years of age. They commented that the regional heterogeneity was found in the infant brain, but local metabolic rate pattern of the children older than 1 year of age is very similar to that of adults. They used arterial or arterialized venous sampling methods whereas other investigators used cardiac region to extract input function in small infant studies. Though exact in terms of absolute regional cerebral metabolic rate, these methods are too invasive to perform on a routine clinical basis. Moreover, when children are 1 year old or older, we usually interpret their images in relative terms not in absolute terms. Clinicians often use the symmetry or asymmetry of FDG uptakes or regional homogeneity as an important guideline to unravel pathologic changes in patients' brains. However, we need more information regarding the subtle age-associated changes that occur in children's brain to differentiate between the normal and the abnormal FDG uptake. As for perfusion of the brain, crude VOI analysis has already been used to determine the relative brain perfusion pattern in 4 to 15 year-old children (Barthel et al., 1997). The cerebral activity uptake, relative to injected dose, was negatively correlated with age. In most brain regions, the counts of

Table 5
Areas with age-associated decreases of FDG uptake in each gender

Regions	L/R	BA	Talairach[a]			T	Cluster size[b]
			x	y	z		
Male							
Ant. limb of internal capsule	L		−22	10	14	5.33	3674
Ant. limb of internal capsule	R		26	3	16	5.15	
	R		28	13	20	5.12	
Inferior temporal region	R	20	42	−30	−27	4.55	1478
Temporal stem	R		40	−5	−18	4.00	
Posterior central region	L		−14	−26	57	4.46	693
Cerebellum	L		−36	−32	−27	4.21	418
Occipital pole	R	18	18	−94	21	4.16	90
Optic radiation	L		−34	−64	5	3.82	114
Female							
Ant. limb of internal capsule	R		32	−1	17	7.11	14,921
Claustrum	L		−30	−15	15	6.44	
Inferior temporal region	R	20	44	−28	−25	5.50	
Inferior temporal region	L	20	−22	−27	−29	4.35	316
Cerebellum	L		−14	−41	−33	3.42	
Temporal stem	L		−40	−3	−23	4.22	436
Optic radiation	L		−26	−65	12	4.19	351

Ant., anterior; BA, Brodmann's area; WM, white matter; L, left; R, right.
[a] Local maxima of clusters composed of more than 10 significant (uncorrected $P < 0.0005$, $T = 3.41$) voxels.
[b] Number of significant voxels (2 × 2 × 2 mm).

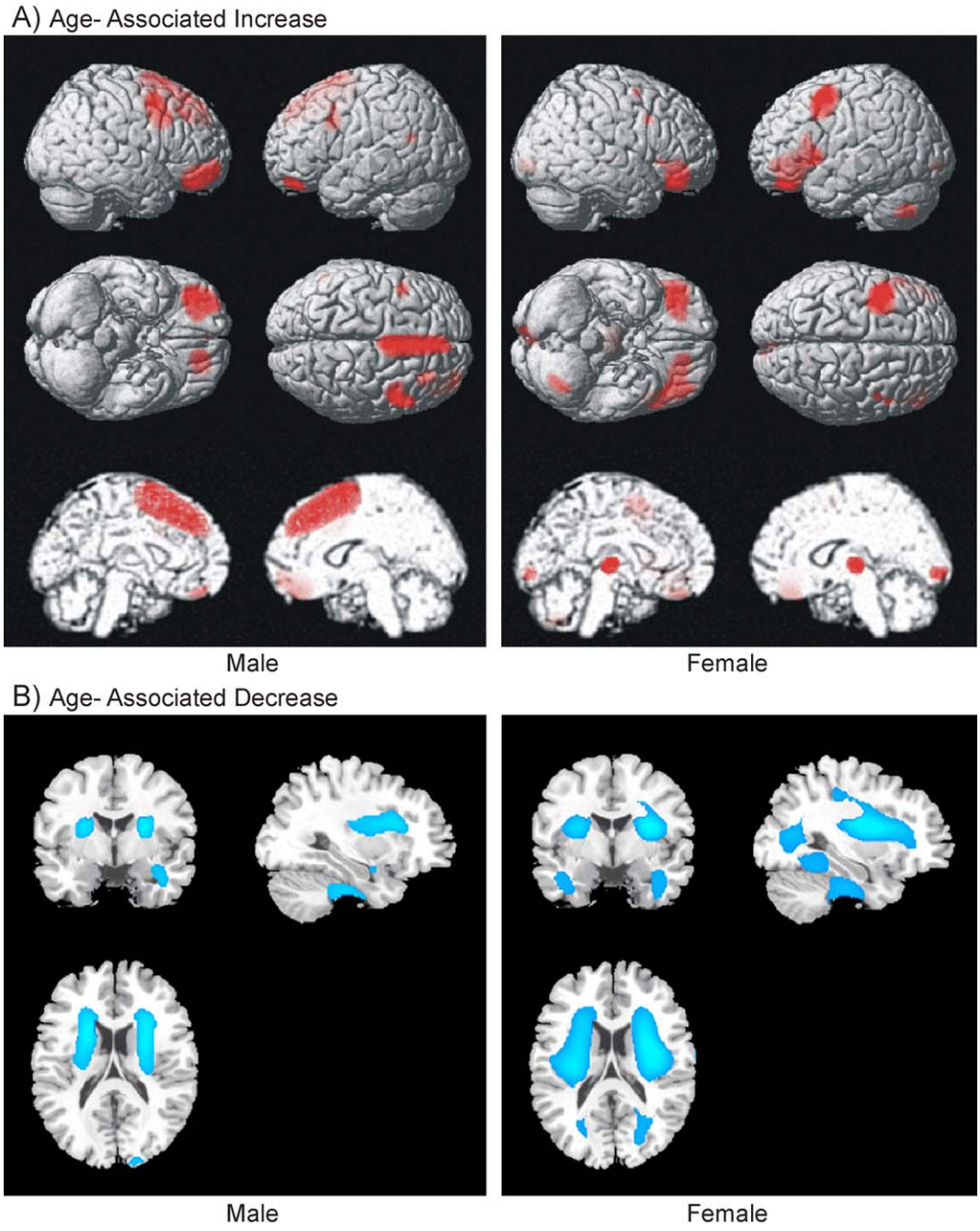

Fig. 3. (A) Rendered brain images showing regions with age-associated increases of FDG uptake in male (left) and female (right) deaf children (for display purpose, $P < 0.005$ uncorrected was used). (B) The brain regions with age-associated decreases of FDG uptake were more extensive in female (left) than male (right) children ($P < 0.0005$).

cerebral blood flows, which were normalized to cerebellar count, were also reported to decrease with increasing age in most cortical regions, including left frontal regions. These findings appeared quite contrary to the findings reported in this study where increases in FDG uptake were observed in various frontal regions. These differences could result from difference in a way to adjust regional cerebral activity. Note that the changes of FDG uptake reported in this study were about the regional glucose activity relative to global brain activity, not about absolute activity level.

Our findings reveal that age-associated changes are mostly symmetric and localized. But our findings do not suggest that, for example, inferior frontal or orbitofrontal FDG uptake count of adult brain itself is higher or lower than that of a 4-year-old child. To make this comparison, we need to perform rather-invasive kinetic studies involving FDG PET in children and to analyze the data as Chugani et al. (1987) did. However, from practical and ethical viewpoints, such further work is not warranted.

It is tempting to think that a 3-fold greater activity of 4-year-old child's in a certain cortex implies that it performs 3-fold more

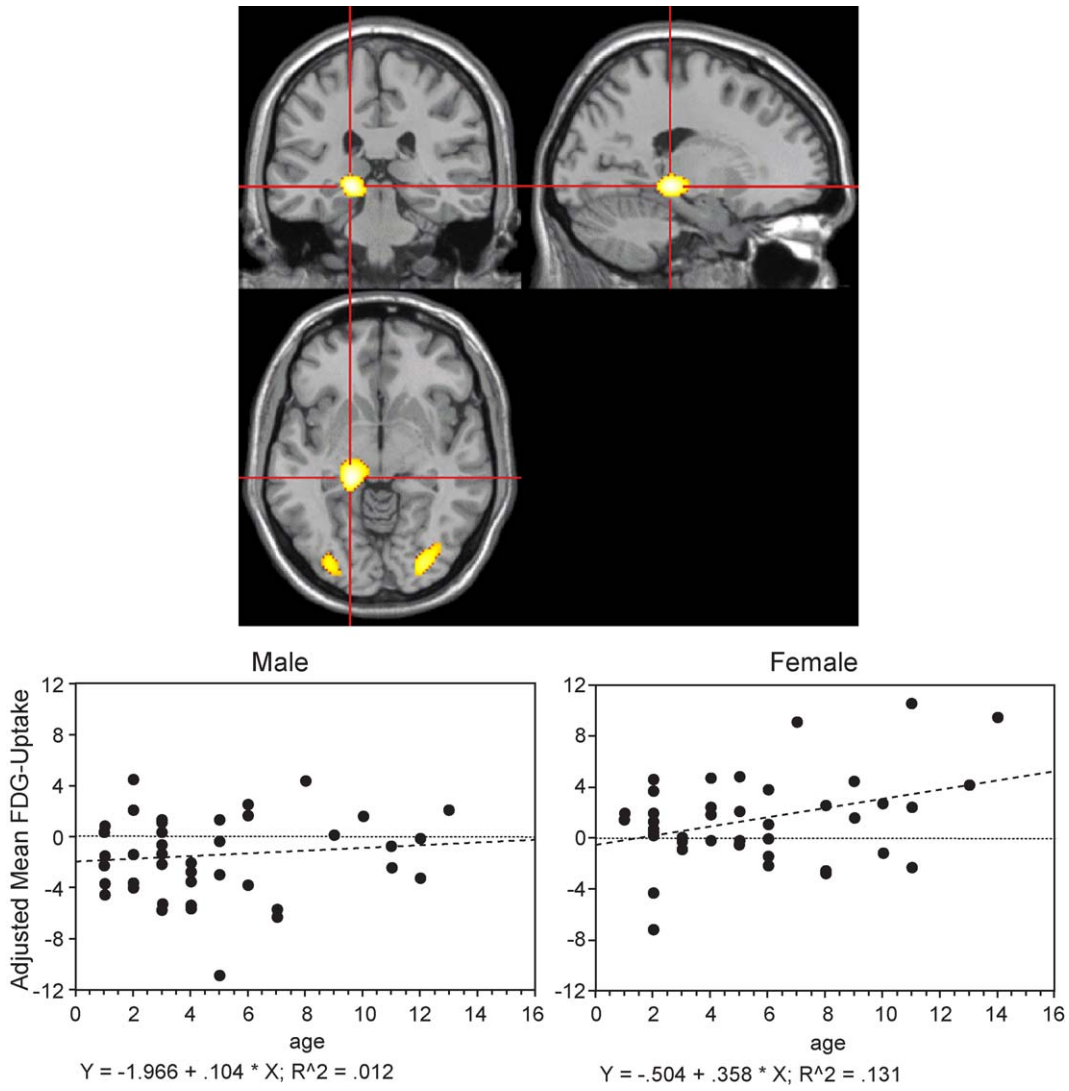

Fig. 4. The female deaf children showed greater overall mean FDG uptake in the left medial geniculate nucleus (Tal $x, y, z = -18, -29, -4$) than the male deaf children.

work than that of adults. It may or may not be the case. We propose that the relative activity of regions of the brain in the same individual is more interesting. If the metabolic activities of some areas change during growth in childhood, then such areas are likely to be associated with ageing and behavioral development, and if not, these areas comply with the global changes of the brain development.

Relative increases of normalized FDG counts in specific areas of the brain including various frontal regions or the thalamus may suggest that these areas become more active with ageing. On the contrary, relative decrease of normalized uptake in inferior temporal areas with increasing age meant that these areas are recruited less during the later childhood than the earlier childhood. We hypothesized that increasing use of certain brain regions represents increasing need and concomitant recruitment and mobilization. We also hypothesized that decreasing use represent increased proficiency and less request for neural resources (at least in gray matters). One might speculate that the age-associated decreasing areas are important more for younger deaf children and that as a child ages, these areas become less recruited. If, smaller brain areas or network are recruited for given functions with greater accommodation and decreased activity will also follow. The behaviors related with these areas with age-associated decreasing activity become more efficient and so smaller neural substrates might be needed for the same tasks.

One should, however, be careful in interpreting the relative increase or decrease of FDG uptake. We would like to emphasize that FDG PET reveals the hourly activity of brain unlike fMRI or activation PET with $H_2^{15}O$. FDG PET activity is the summed average of over one hour or so brain activity. Because of these characteristics of FDG PET, the FDG PET results disclose the long-term steady-state findings of brain–behavior relations. Not only changes in synaptic activity, but also changes in synaptic density (anatomical/physiological development involving synaptic formation) or in the density of glucose transporters could be shown with changes in metabolic activity.

In this study, we found significant negative correlations between FDG uptake and age in the well-known white matter regions (such as corpus callosum, internal capsule, optic radiation, or temporal stem). FDG uptake, detected in white matter

regions, is extremely small amount since FDG uptake occurs mostly in gray matter coexisting with white matter in a given resolution of PET image study (partial volume effects). Although myelination of long association and commissural fiber systems in telencephalon is known to last until the end of the first decade of life, myelination of major fiber system mediating sensory input to the thalamus and cerebral cortex seemed to complete early in development (Sampaio and Truwit, 2001). Therefore, the negative correlations here might be asso-ciated with increasing myelination due to normal development. The meaning of these associated changes is not known. However, a possibility should be considered that myelination continued due to use-dependent changes in brain. We found the female deaf children showed this type of FDG uptake decrease with growth in the greater extent than the male children.

Nonlinear changes

As was previously often observed in age-associated brain morphology (Good et al., 2001), age-associated changes in brain glucose metabolism were not always linear. In a previous study (Van Bogaert et al., 2000) where nonlinear age effects were investigated in subjects ages 6–38 years, reported were linear increases of the adjusted glucose metabolism before the age of 25 even in the brain structures showing nonlinear changes such as the thalamus or the anterior cingulated cortex. Therefore, we found mostly linear changes rather than nonlinear changes of glucose metabolism in various brain regions, given the age range used in this study. Putamen or white matter regions in basal ganglia were the only exceptions showing early decrease followed by an increase. These features all required explanation in terms of behavioral, cognitive, and/or emotional developments, but are beyond the scopes of our present investigation.

Sex difference

We found distinctive pattern of age-related FDG uptake changes in each gender. For example, the male children showed more linear increase in the right dorsomedial frontal region while the female children in the left dorsolateral prefrontal region, mediodorsal thalamus bilaterally, and the left cerebellar cortex. Further research will be needed to determine if these gender differences found in the age-associated changes of FDG uptake are associated with gender difference in developmental rate in specific behavioral/cognitive functions. Note that these sex differences discussed here were in terms of the sex difference in the rate of FDG uptake increases with age, not the difference in the average amount of FDG uptake itself between two sexes.

The dorsomedial frontal gyrus is often suggested in association with attentional control (Benedict et al., 2002; Giraud et al., 2004; Lucchetti et al., 1998; Small et al., 2003) or social cognition (Mundy, 2003). Therefore, we speculate that the male children's ability to control attention to external stimuli or social cues might increase with age during developmental years. If the age-associated increase in the right medial frontal region is associated with the attentional control ability, one might expect to speculate the sex difference in this cognitive/behavioral attribute to interact with age. For example, the deaf children showed greater peripheral attention and less central attention to visual stimuli unlike to normal-hearing children (Proksch and Bavelier, 2002). It will be interesting to investigate how age and gender influence this type of attentional characteristics in deaf as well as normal children.

Although there was not much sex difference in the right dorsolateral prefrontal regions, the left dorsolateral prefrontal region showed sex difference between the male and female deaf children in the age-associated changes of FDG uptake. The dorsolateral prefrontal cortex has been known to be involved in sustained attention (Toichi et al., 2004) or working memory (Rypma and D'Esposito, 2003). The increased FDG uptake with maturation in the left dorsolateral prefrontal regions might also be consistent also with the findings with some volume studies in adults. Females were found to have larger volumes in language-related regions including the dorsolateral prefrontal cortex and superior temporal gyrus in the dominant hemisphere than male (Harasty et al., 1997; Schlaepfer et al., 1995). These findings were consistent with the notion that female is known for better verbal ability than male. It was often reported that female deaf or hard-of-hearing children showed better language outcome than the male in response to auditory–verbal intervention (Easterbrooks and O'Rourke, 2001).

We also observed that the average FDG uptake in the female was greater than the male in the left medial geniculate nucleus (MGN) (Fig. 4) and in small occipital regions in both hemispheres. Considering MGN is one of the subcortical structures in the auditory pathway, the left MGN might have been recruited for other sensory function in the female deaf children but not in the male deaf children. In other words, a phenomenon so-called cross-modal 'brain plasticity', which is usually observed following sensory deprivation (Rauschecker, 1999), might take place more in the female than male deaf children. Greater FDG uptake in higher visual cortex in the female deaf children in comparison to the male also supports the idea of cross-modal plasticity. It is again worthy to note that the sex difference was found in the MGN region of the left hemisphere only.

Some recent investigations reproduced results of earlier Chugani's report in infants by calculating absolute glucose metabolic rates in crude and large VOIs (Kinnala et al., 1996). In the epilepsy patient population, Van Bogaert et al. (2000) found age-associated increases of brain glucose uptake in the thalami and cingulate gyri. The extrapolation of their findings to normal population was premature as in this study, since the glucose uptake of their population could be influenced not only by the children's pathology, that is, epilepsy, but also by their antiepileptic medication as well. At least in the present investigation, the confounding effect of medication was absent.

In summary, we suggest that the inferior frontal/orbitofrontal areas increase their metabolic activity during growth in the brains of deaf children during development. The right dorsomedial frontal region in the male and the left dorsolateral prefrontal region, thalamus, and left cerebellum in the female deaf children showed gender-specific increases with maturation. In the female deaf children, the FDG uptake in the left MGN and small areas of middle occipital regions was greater in comparison to the male deaf children.

These age-associated changes found in this study could reflect normal development occurring in the deaf children during maturation. If this is the case, differences between the child's brain versus the adults' brain or the control group poorly matched in age and/or sex, differences between groups should be interpreted with caution. However, it is equally possible that the results reported here reflect the changes specific only to deaf children during

developmental years. The increases of FDG uptake in orbitofrontal or inferior prefrontal regions might be specific to deaf children. In our previous FDG PET study where the postlingual adult deaf was compared with normal hearing adult (Lee et al., 2003), the inferior prefrontal cortex and hippocampal region were among the brain areas showing deaf induced hypometabolism. Any regions close to or included in those brain regions could be considered as brain areas showing deaf-specific age-associated changes, rather than normal development, despite the direction of changes (increase vs. decrease).

In spite of differences in deaf type and age between the postlingual adult deaf in a previous study (Lee et al., 2003) and the pre- or perilingual (i.e., early onset) deaf children used this study, we speculate that the age-associated changes found in the orbiofrontal and inferior prefrontal regions may have represented the changes adapting to the deaf condition during the developmental years in the deaf children. The decrease change in parahippocampal region (VOI analysis) might also be associated with deaf condition.

We also speculate that the sex differences in the time course of development in the deaf children reported here could be comparable with that of the normal development in normal hearing children since we do not have any reason to believe the existence of a gender effect only specific to deaf population. The male-specific changes in the right medial prefrontal and the female-specific changes in the left dorsolateral prefrontal and mediodorsal thalamus could be considered as gender differences, which might be observed in normal development as well. Yet when the gender-specific differences were found in sensory pathways like the MGN (auditory), or occipital regions (vision), there seemed to be a possibility that female deaf children have greater cross modal plasticity than male children.

Further investigations will need to carefully examine the relationship between function of these brain regions and known cognitive or behavioral sex differences in normal and deaf children during the developmental years both/either in normal and/or deaf children.

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