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Developmental hemispheric asymmetry of interregional metabolic correlation of the auditory cortex in deaf subjects

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Abstract

The functional connectivity of the auditory cortex might be altered in deaf subjects due to the loss of auditory input. We studied the developmental changes of functional connectivity of the primary auditory cortex (A1) in deaf children, deaf adults, and normal hearing adults by examining interregional metabolic correlation with ^{18}F-FDG PET. The mean activity of FDG uptake in the cytoarchitectonically defined A1 region served as a covariate in the interregional and interhemispheric correlation analysis. A1 metabolic rate was correlated with that of the ipsilateral superior temporal lobe in both normal and deaf subjects. This correlated area was larger in deaf children than in deaf or normal hearing adults. Concerning the functional connectivity of A1, a hemispheric asymmetry was found in that the extent of interregional correlation was clearly larger in the right than in the left hemisphere. This asymmetry was particularly pronounced in the younger deaf children. Both extent and asymmetry of the functional connectivity of A1 subsided with age. Contrary to this, a correlation between the left and the right primary auditory cortices was absent in younger deaf children but became apparent as they grew older.

Introduction

Early perception of auditory information is critical for the normal development of the auditory cortex and its connections with other brain regions (Truy, 1999). The auditory cortex develops in association with related cortical areas. Interregional and cross-callosal correlations develop or subside with age, and regional organization and functional connectivity are achieved in adults. Synaptic revision and intermodal or top-down modulation both play roles throughout early development, during which A1 and related brain regions become engaged in auditory processing and language functions. Unlike normal hearing children, deaf children might show unusual interregional correlations due to the differential growth of the diverse sensory modalities.

While auditory cortical glucose metabolism decreases in postlingual deaf adults (Ito et al., 1990), in deaf children it can vary widely depending on individual characteristics (Lee et al., 2001; Catalan-Ahumada et al., 1993; Hirano et al., 2000). This individual variation was correlated with the degree to which hearing and speech capabilities were recovered following cochlear implantation (Lee et al., 2001). Before implantation, metabolism in auditory cortex was decreased initially but recovered later, which might indicate cortical plasticity either of the same (cross-modal), lower (bottom-up), or higher level (top-down) reorganization. Auditory cortical hypermetabolism could indicate greater synaptic density due to either a delayed or an absent synaptic pruning by auditory deprivation during early developmental age (Hirano et al., 2000). Greater synaptic density is, in turn, associated with greater glucose metabolism (Chugani et al., 1987; Chugani, 1998).

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Table 1
Deaf and normal hearing control groups

Group	*N*	Mean age (SD)	Age range	Sex (M/F)	Deaf onset		Duration	Etiology
					Early	Late		
Younger deaf children	64	3.42 (1.68)	1–6	35/29	64	0	3.32 years (1 month–6 yr)[a]	Unknown, 37 Congenital, 16 Meningitis, 10 Accident, 1
Older deaf children	27	10.22 (2.21)	7–15	12/15	24	3	8.71 years (1 month–13 yr)[a]	Unknown, 8 Congenital, 15 Meningitis, 2 Chicken pox, 1 Mumps, 1
Deaf adults	20	35.00 (13.72)	16–56	10/10	6	14	10.28 years (1 month–53 yr)[a,b]	Unknown, 14 Chronic otitis media, 3 Meningitis, 2 After febrile illness, 1
Normal hearing	21	26.71 (8.80)	19–56	16/5	—	—	—	

[a] Duration was approximated as age for the early onset (congenital or unknown).
[b] Not included one patient whose duration is not clear due to unclear profound deaf onset.

The synaptic density within the primary auditory cortex in either hemisphere as well as the connectivity between A1 and other brain regions might differ between deaf and normal hearing subjects. That is, the way in which A1 is functionally connected to other brain regions in deaf subjects may or may not be different from normal hearing individuals. Examination of the interregional relationship of the auditory cortex (A1) with other brain areas in deaf subjects would provide an opportunity to study the developmental changes in the functional connectivity of A1 both within and between hemispheres (Schreckenberger et al., 1998).

Precise anatomical delineation of the auditory cortex, however, is a prerequisite for an interregional correlation analysis. Fortunately, a stereotactic probabilistic map of cytoarchitectonic area Te1 was recently published (Morosan et al., 2001; Rademacher et al., 2001). This map is based on an observer-independent definition of cytoarchitectonical borders in a sample of 10 human postmortem brains (Morosan et al., 2001; Rademacher et al., 2001). In this study, using this probability map as a spatial template (covariate), interregional metabolic correlation of A1 was examined in an objective manner.

In order to understand how the deprivation of auditory input in deaf subjects influences interregional or cross-callosal functional connectivity during development, we examined four groups: two deaf children groups (younger deaf children who are 6 years old or younger and older deaf children from 7 to 16 years old), a postlingual deaf adult group, and a normal hearing adult group.

Materials and methods

^{18}F-FDG positron emission tomography (PET) scan was performed for the deaf patient as a clinical presurgical evaluation in the Seoul National University hospital since the PET results served as an inclusion criterion for cochlear implantation surgery (Lee et al., 2001). Sufficient and detailed explanations for the procedure, risk, and purpose/benefit of FDG-PET study as an evaluation method for prediction of postsurgical outcome were given to the adult patients or the parents of child patients by clinicians while the other presurgical test procedures were explained. PET scan was performed only for the individuals either who or whose parents wanted to take FDG-PET as a presurgical evaluation test and gave the informed consents. The patients who did not agree due to various reasons or the others who were considered by surgeons as too old for good surgical outcome skipped the PET study. For the current study included were the PET studies from 91 pre/perilingual younger deaf children (88 early onset and 3 late onset) and 20 postlingual deaf adults (35 years +/− 13.7; 6 early onset and 14 late onset). The deaf children were divided into two groups: one for younger deaf children who were 6 years old or younger ($n = 64$; mean age: 3.4 years +/− 1.7) and the other for older deaf children who were older than 6 but younger than 16 years old ($n = 27$; mean age: 10.2 years +/− 2.2). All the deaf patients included in this study were the profound deaf with or without known etiology of deaf, but not with other apparent neurological/psychiatric symptoms (Table 1). ^{18}F-FDG PET was also obtained from 21 normal hearing volunteers (26.7 years +/− 8.8) who gave their informed consent before participation.

^{18}F-FDG PET scans were performed using an ECAT EXACT 47 PET scanner (Siemens-CTI, Knoxville, TN), with an intrinsic resolution of 5.2 mm FWHM (full width at half-maximum). Images were simultaneously collected of 47 contiguous planes with a thickness of 3.4 mm, to give a 16.2-cm longitudinal field of view. Before FDG administration, transmission scanning was performed using three

Ge-68 rod sources for attenuation correction. Static emission scans were started 30 min after the injection of 370 MBq ^{18}F-FDG and continued for 30 min in the resting state. No earplugs were used during the PET scans for normal subjects, and they were scanned under normal environmental noise of the scanner room. Transaxial images were reconstructed using a filtered back-projection algorithm with a Shepp-Logan filter at a cutoff frequency of 0.3 cycles/pixel as 128 × 128 × 47 matrices of size 2.1 × 2.1 × 3.4 mm. Once converted to analyze format, the PET images were spatially normalized to an MNI template, smoothed (FWHM 16 mm) using SPM99. 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. A probabilistic map of the right and left Tel areas (Morosan et al., 2001; Rademacher et al., 2001) was converted into MNI space. This probabilitic map of the primary auditory cortex (A1) was used to define our volume of interest (VOI) in the normalized and smoothed PET image.

A mean count of the FDG uptake in the VOI of the A1 region was obtained from each hemisphere and the FDG uptake count was subjected to three different types of statistical analyses:

1. The mean counts of FDG uptake of the A1 of each hemisphere were compared between the four groups (deaf younger children, deaf older children, deaf adults, and normal hearing controls) in order to test whether significant group differences exist in A1 glucose metabolism.
2. The mean count of FDG uptake of each A1 served as a covariate for interregional correlation analyses, in which voxels showing a significant correlation with the covariate were searched for within the whole brain. Clusters containing more than 100 contiguous voxels each with a significance of $P < 0.05$ (corrected for multiple comparison) were used to determine the extent of the functional connectivity of the A1. Interregional analysis was performed for the A1 of the left and right hemispheres for each of the four groups. Only the sizes and local maxima of the significant clusters are described in this paper.
3. The mean count of FDG uptake of the A1 in each hemisphere was subjected to a correlation analysis for each group. Correlation between the mean count of FDG uptake in left A1 and that of right A1 was examined in order to study interhemispheric functional connectivity between the A1 of each hemisphere.

Results

Adult deaf subjects showed a significantly lower metabolism within the A1 (54.2 ± 0.49 in left; 54.0 ± 0.66 in right) than normal hearing adults (55.9 ± 0.28 in left; 55.6 ± 0.33 in right) ($P < 0.05$, Fig. 1). The average glucose metabolism of either deaf children group was not significantly lower than normal hearing adults.

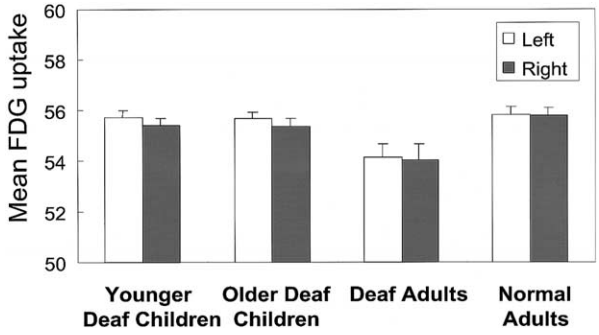


Fig. 1. Mean glucose metabolism in the primary auditory cortex (A1), which was defined for each hemisphere by means of a probability map of area Te1 (empty bar: left hemisphere; filled bar: right hemisphere). Mean and standard error were shown for all four examined groups, including younger deaf children, older deaf children, deaf adults, and normal hearing adults.

In all subjects, the ipsilateral superior temporal lobe showed a significant positive correlation with A1, which is probably due to interregional autocorrelation ($P < 0.05$, corrected for multiple comparison, Fig. 2, Table 2). In the younger deaf children, positive correlation not only encompassed the primary auditory cortex but also included the entire superior temporal gyrus and part of the middle temporal. The interregional correlation of right A1 was more extensive, including not only the temporal gyri but also posterior insula and dorsolateral prefrontal regions. The correlated regions in the right hemisphere extended caudally to parts of the parietal cortex (Fig. 2, top row).

The size of the positively correlated voxel clusters in the right hemisphere was greater than in the left hemisphere in all groups (Fig. 3). This hemispheric asymmetry of the functional connectivity of the A1 was particularly striking in both younger and older deaf children. Considering the cortical regions outside the superior temporal gyrus, the extent of interregional correlation of the A1, in particular right hemisphere, seemed reduced with advancing age in deaf patients (Fig. 4).

We also found that metabolism of the left A1 was correlated not only with the ipsilateral but also with the contralateral superior temporal lobes in deaf adults, unlike younger deaf children or normal hearing adults (Fig. 3, third row). This A1 cross-hemispheric correlation was further analyzed with the FDG counts of both A1 regions in each hemisphere. Correlations between the left and the right A1 FDG uptake counts are shown in Fig. 5. There was found an apparent correlation in the older (7–15 years old) deaf children group ($r^2 = 0.332$, $P < 0.002$). The A1 cross-hemispheric correlation was even greater in the adult deaf patient group ($r^2 = 0.602$, $P < 0.0001$). There was, however, no significant correlation in the younger deaf children group or the normal hearing group.

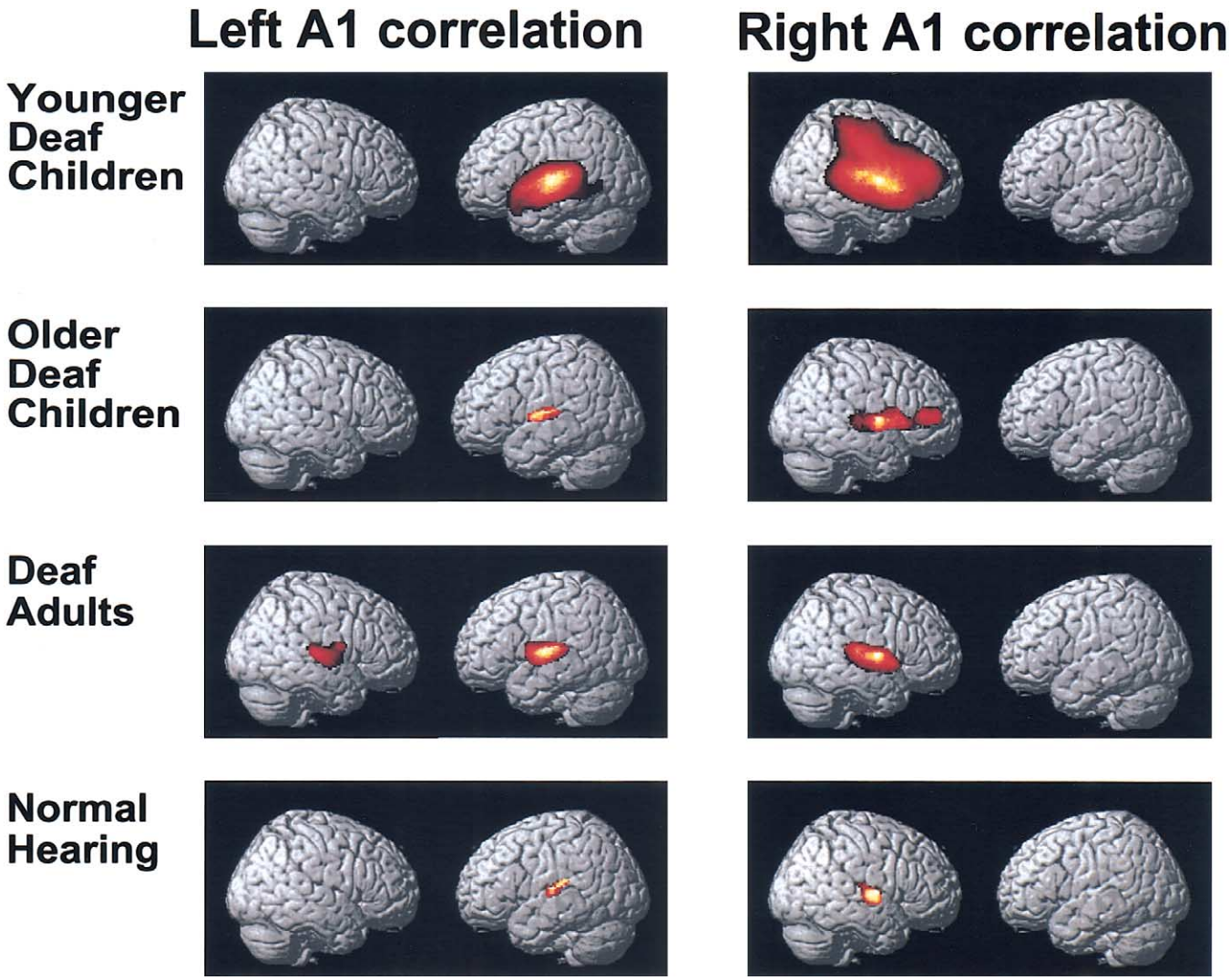
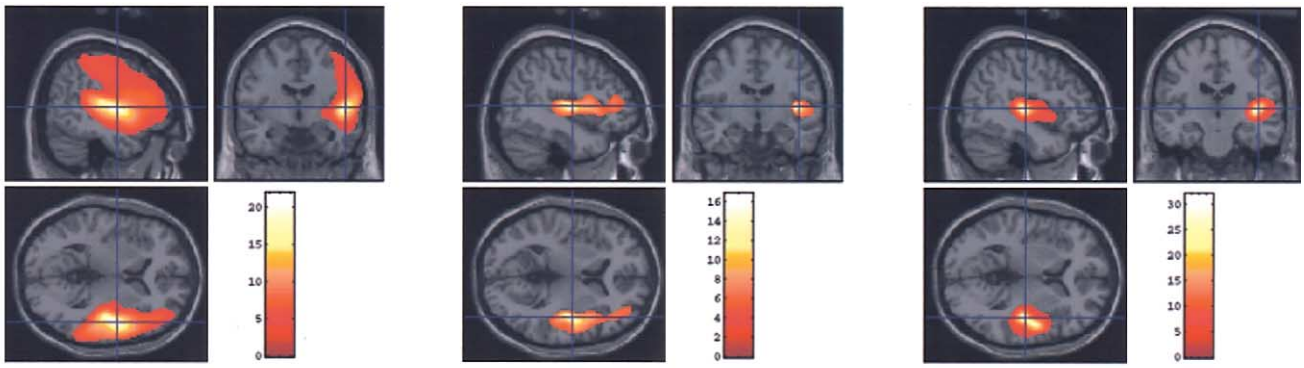


Fig. 2. The extent of cortical regions showing a positive correlation ($P < 0.05$ corrected) with the glucose metabolism of A1 for each hemisphere. Deaf children groups showed the largest cluster, particularly in the right hemisphere. Conversely, normal hearing adults presented the smallest correlation clusters. The group of adult deaf subjects occupied an intermediate position concerning the size of clusters positively correlated with A1.

Discussion

Our findings based on the deaf children data suggest that the functional connectivity of the primary auditory cortex with adjacent regions was more extensive in right hemisphere than in left and it decreases with advancing age. The extensive connectivity found in deaf children was greater in younger than in older children. No evidence indicating functional connectivity between the left and the right A1 was found in younger deaf children. The cross-hemispheric connectivity was observed only with advancing age in deaf children (older deaf children group) and was greatest in deaf adults. The high correlation between the left and the right A1 metabolism in deaf adults was in contrast to the absence of correlation in normal hearing subjects. These findings might indicate that the functional connection between both hemispheres' A1 areas was at least influenced by the loss of auditory input in deaf adults and also in older deaf children. It is not clear why interhemispheric connectivity emerges between the A1 areas of both hemispheres and why extensive connectivity with the ipsilateral hemisphere subsides with advancing age in deaf children. We would speculate that developmental changes of connectivity of the A1 might be an exaggerated or at most a deviant phenomenon of the developmental pattern in normal children (Innocenti, 1981).

The prominent hemispheric asymmetry concerning functional connectivity was found in the deaf children of this study. The right primary auditory cortex was more extensively connected to the ipsilateral temporal and frontal lobes than the left primary auditory cortex. This functional connectivity subsided with age. Without data from normal children which are very hard to obtain because of ethical problems, it is difficult to conclude if this hemispheric asymmetry is comparable to the course of normal development or associated uniquely with sensory deprivation. At least, the advancing age affects the functional connectivity



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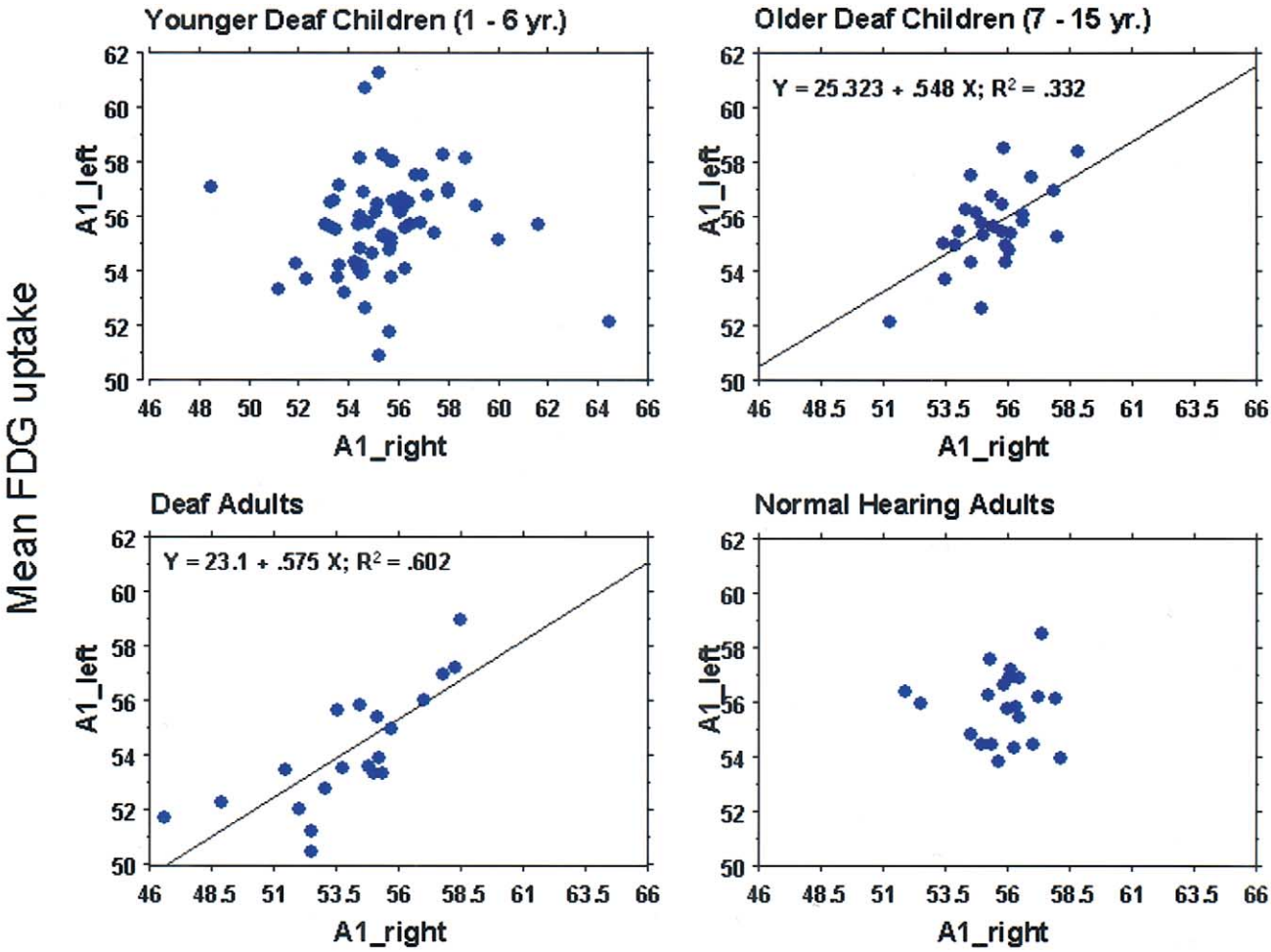

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Fig. 4. Functional correlation of right A1 was reduced with advancing age in deaf subjects, as indicated by the reduction of clustered voxels showing a significant interregional connection.

Fig. 5. Interhemispheric correlations of the glucose metabolism count in the primary auditory cortex, i.e., A1 between two hemispheres. The points of scattergram represent data from each individual subjects whose mean glucose metabolism count (normalized to the mean FDG uptake of the whole gray matter, which was 50) of A1 in left hemisphere is shown in the *Y* axis and that of right hemisphere in the *X* axis. Significant interhemispheric correlations were found in the older deaf children group and in the deaf adults group to a greater extent, but not in the younger deaf children or normal hearing adults groups.

Table 2
Brain regions of positive correlation with A1 activity

Group	N*	Reference	L/R†	Region included	BA‡	Talairach coordinate			T
						x	y	z	
Deaf children younger (<= 6 years)	64	Left A1	L	Superior temporal[a]	41	−40	−19	8	28.29
				Middle temporal	21	−57	−58	5	4.56
				Inferior temporal			Included		
		Right A1	R	Superior temporal[b]	41, 22	50	−6	4	21.89
				Middle temporal			Included		
				Inferior temporal			Included		
				Inferior prefrontal	46		Included		
				Middle prefrontal	10		Included		
				Post central/inferior parietal			Included		
Deaf children older (> 6 years)	27	Left A1	L	Superior temporal	41	−40	−21	8	14.51
				Superior temporal	22	−48	−6	6	7.67
		Right A1	R	Superior temporal	22, 41	44	−9	6	16.83
				Inferior prefrontal	46	42	35	6	6.88
				Middle prefrontal	10	38	49	7	6.29
Deaf adults	20	Left A1	L	Superior temporal	41	−48	−9	8	21.73
						−44	−21	8	21.67
			R	Superior temporal	42	59	−19	8	7.16
				Precentral	4, 6	53	1	13	6.98
		Right A1	R	Superior temporal	41	44	−17	5	31.97
					22	50	−8	4	29.94
Normal control	21	Left A1	L	Superior temporal	41	−44	−17	10	12.46
						−53	−26	16	7.45
			R	Superior temporal	41	48	−13	4	17.18

* Number of patients; † left, mid, or right ‡ Brodmann area; ¶ Local maxima (8.0 mm apart per cluster) of clusters which were composed of 100 contiguous significant voxels ($P < 0.05$ corrected for multiple comparison at voxel level).

[a] Cluster also included insula.

[b] Cluster also included insula and inferior prefrontal regions.

of ipsilateral cortical regions with right A1, which is quite different from the increasing functional connection between homologous primary auditory cortices of both hemispheres with advancing age in deaf children. With advancing age in deaf children, the A1 functional connectivity with ipsilateral cortical regions became similar to the pattern of the normal adults, whereas the interhemispheric connectivity of A1 became similar to that of the deaf adults.

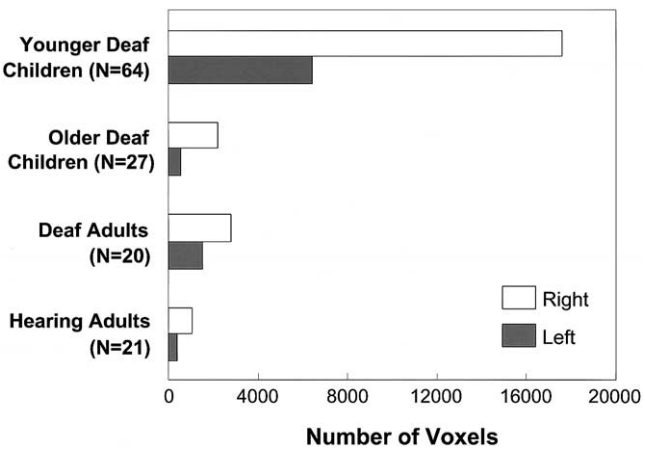

Fig. 3. The size of ipsilateral clusters (number of voxels) with a positive correlation with the A1 of each hemisphere (empty bar: left hemisphere; filled bar: right hemisphere).

Taken together, this might indicate that, in the very early age, the ipsilateral adjacent cortical areas in right hemisphere are more closely coupled with the primary auditory cortex. Interestingly, functional connectivity of A1 in the left hemisphere, known as being specialized for verbal function, was rather restricted. Left hemispheric cortices were less closely coupled with the primary cortex and might have been independent from A1 since the very early age in deaf children (Holowka and Petitto, 2002). This asymmetry in functional connectivity seems to be in accord with the known facts of hemispheric asymmetry in the literature. For example, the right hemisphere is known to be more specialized in acoustic (sound) processing whereas the left one is specialized in phonological (language) processing (Hugdahl, 2000; Hugdahl et al., 1999; Zatorre et al., 1994). Left hemispheric language processing areas might be less tightly coupled with A1 in very young subjects. As children grow, left hemispheric language regions become engaged with the auditory cortex in normal individuals but with other relevant cortices in deaf subjects. Language-related regions could be connected even with visual cortices in deaf subjects as a consequence of cross-modal plasticity (Giraud et al., 2001; Rauschecker, 1999). Dichotic listening studies have indicated an asymmetry in the modulatory role of the auditory cortex on peripheral acoustic asymmetry (Hugdahl, 2000; Khalfa et al., 1997, 2001). Our data present evidence that

developmental hemispheric asymmetry exists in auditory and related cortices in a large cohort of deaf subjects and, therefore, possibly in normal hearing children.

Based on the observations discussed above, we propose the following developmental sequence in A1 functional connectivity. A1 shows a transition from extensive to restricted functional connections with adjacent cortical areas during development. The way in which A1 was connected with other brain regions differed between both hemispheres, probably due to a predetermined hemispheric asymmetry in A1's functional connectivity as from a very early developmental age. In normal subjects, functional connection of A1 with other cortical regions must have been established with areas of the same or different hierarchical levels. In deaf subjects, lacking a normal auditory input, synaptic revision is inadequate, which results in exaggerated functional connectivity enabling intervention of cortical plasticity. With advancing ages, A1s in both hemispheres might be susceptible to common factors of brain plasticity, which could be either/both from cortical or/and subcortical origin (Bavelier and Neville, 2002). The interplay between top-down and bottom-up cortical plasticity in sensory cortices must be part of normal development but is exaggerated in deaf subjects.

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