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Changes in the functional connectivity of auditory and language-related brain regions in children with congenital severe sensorineural hearing loss: An fMRI study

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ABSTRACT

Early hearing deprivation can affect the development of hearing, language, and vision. Thirty-four infants with congenital severe sensorineural hearing loss (CSSHL) and 20 age- and sex-matched subjects with normal hearing were recruited. The amplitude of low-frequency fluctuation (ALFF) of auditory and language-related brain areas was compared between infants with deafness and control subjects. Relative to subjects with normal hearing, infants with CSSHL had decreased ALFF values in the right Brodmann's area (BA) 22 region and in parts of several language-related regions. As the duration of hearing loss increased, the ALFF values in the left auditory and linguistic brain regions increased. These findings indicate that hearing deprivation affects the functional connectivity between auditory and language-related brain regions and the corresponding sensory and visual functional brain regions and that this functional connectivity decreases as the duration of hearing loss increases. Cochlear implantation performed after 24 months may limit the habilitation of hearing and speech functions due to functional reorganization of the auditory and linguistic brain areas over time.

1. Introduction

Organic lesions of the inner ear hair cells, the stria vascularis, the spiral ganglion, the auditory nerve, or the auditory center can hinder sound perception and analysis and influence the transmission of sound information. The hearing decline or hearing loss arising from such lesions is called sensorineural hearing loss. The main cause of congenital sensorineural hearing loss (CSNHL) is damage to or absence of the inner ear hair cells such that the auditory nerve cannot produce nerve impulses. The incidence of congenital hearing loss in children is approximately 1/1000, and half of the cases are hereditary (Greinwald & Hartnick, 2002). Autosomal recessive inheritance is the most common mode of transmission (Morton, 1991). A survey showed that approximately 60 babies with sensorineural deafness are born each day in the United States, and the prevalence can reach 1‰–3‰ (Nagapoornima et al., 2007).

Cochlear implantation (CI) is an effective method for restoring hearing in individuals with severe or extremely severe sensorineural hearing loss (Niparko et al., 2010). This treatment can enable normal speech and language development (Zheng, Wu, Huang, & Wu, 2017). The factors affecting CI include the duration of hearing loss, the age of onset of hearing loss, the age of the recipient at the time of implantation, and the duration of hearing-aid use. Among these factors, the age at the time of CI is considered the most

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important factor affecting the success of CI. In children with congenital and early-onset hearing loss, higher-order auditory cortices do not have the opportunity to develop normally unless adequate auditory stimulation is received, usually via CI (Sharma, Campbell, & Cardon, 2015). Through follow-up, Govaerts et al. (2002) found that children with deafness benefited from CI before the age of 6 years. CI before the age of 2 years was found to be effective for language and hearing rehabilitation. To avoid the irreversible loss of auditory performance, surgeons typically place the implants when the child is between 2 and 4 years of age. A study (Sharma, Nash, & Dorman, 2009) suggested that the variation in rehabilitation capacity with implantation age may be due to the functional reorganization of the auditory and language-related brain regions over time. At present, standard imaging examination can show whether the structure of the inner ear is abnormal, but it is difficult to evaluate the nature of the lesion and the changes in the morphology and function of the auditory cortex, the auditory system, and the language pathway. The auditory cortex and its functional status are not reflected in such examinations.

Analysis of the ALFF (Zang et al., 2007) is a data-driven analysis method that has developed rapidly in recent years. This method can reflect the level of spontaneous neuronal activity in the resting state (Zuo et al., 2010). In the resting state, the brain regions of the default mode network have the highest rates of glucose metabolism and blood flow (Raichle & Snyder, 2007) and the highest ALFF values (Zang et al., 2007; Zuo et al., 2010). Analyses of functional connectivity, measured as linear correlation, are used to examine the temporal correlations of BOLD signal fluctuations between spatially distant regions of the brain. Tian et al. (2006) and other research groups have found that the risk of attention deficit hyperactivity disorder (ADHD) is significantly increased in children with strong functional connectivity between the dorsolateral anterior cingulate cortex (dACC) and the bilateral pons, insula, cerebellum and thalamus. This observation suggests that in the absence of a certain sensory pattern, the functional connectivity between different associated brain regions changes.

According to the basic principle of ALFF analysis (Zang et al., 2007), which assumes that the brain BOLD signal has physiological significance in the low-frequency range, the average value of amplitudes at all frequency points within a frequency band (0.01–0.08 Hz) is used to characterize the strength of a voxel's spontaneous activity. ALFF reflects the level of spontaneous activity of each voxel from the perspective of energy. Studies have attributed low-frequency fluctuations to spontaneous neuronal activity, but the relationship between these two phenomena is not very clear. By simultaneously recording electrophysiology and fMRI signals, Logothetis, Pauls, Augath, Trinath, and Oeltermann (2001) found that task-based BOLD signal changes and local field potential (LEP) ratios are more closely related to a single peak potential, suggesting that BOLD reflects the integration of information input with the internal processing of the cortex rather than simple spike output. Based on the above findings, it was hypothesized that the low-frequency fluctuation of the resting state fMRI should have the same potential electrophysiological mechanisms as the task-based fMRI BOLD signals. According to this hypothesis, ALFF can be considered to reflect spontaneous neuronal activity.

Although ALFF is generally considered to reflect spontaneous neuronal activity in the brain, the relationship between ALFF and this activity is not yet fully clear. The following three observations indirectly support the existence of a relationship between these two factors. First, the ALFF value of gray matter is approximately 60% higher than that of white matter (Zuo et al., 2010). This disparity is consistent with the difference in the BOLD signals between the two tissues; the gray matter of the brain is mainly composed of neuronal cell bodies and dendrites, whereas white matter is mainly composed of nerve fibers. Thus, ALFF may be a sign of local spontaneous neuronal activity. Second, the ALFF value of the visual cortex is significantly higher during blinks than when the eyes are steadily closed, which is consistent with the fact that neuronal activity is higher in the former case than in the latter (Yang et al., 2007). Third, in the resting state, the highest ALFF value is in the default network brain region (Zang et al., 2007; Zuo et al., 2010). PET examination also shows that brain blood flow and glucose metabolism are highest in the brain regions of the default mode network (Raichle & Snyder, 2007). Cerebral blood flow and glucose metabolism can indirectly reflect the level of brain activity, indicating that ALFF can also indirectly reflect spontaneous brain activity in the brain.

This study aimed (i) to investigate the changes in ALFF in the auditory and language-related brain regions of sedated children aged 6–48 months with congenital extremely severe sensorineural hearing loss to evaluate the functional reorganization of the auditory cortex and language-related brain regions before CI, and (ii) to investigate whether children with deafness and children with normal hearing differ in the extent of brain connections between the auditory and language-related brain regions and the whole brain.

2. Materials and methods

2.1. Participants

Based on the inclusion and exclusion criteria, a total of 34 infants (including 21 males and 13 females) with congenital severe sensorineural hearing loss (CSSHL) who did not pass hearing screening using the auditory brainstem response (ABR) test at 3 days and 42 days after birth were retrospectively included in our study. The ABR results of all infants were greater than 95 dB, which indicates severe or profound sensorineural hearing loss. The ages of the infants with deafness at MRI examination ranged from 6 months to 48 months (mean age 24.18 ± 14.00 months). The exclusion criteria included a variety of central nervous system diseases. None of the infants had any history of ear surgery or ototoxic drug therapy. Twenty (including 12 males and 8 females) age- and sex-matched normal hearing subjects were recruited. The ages of the control subjects at MRI examination were 6 months–48 months (mean age 26.82 ± 4.17 months). The infants in the control group did not have any central nervous system diseases. Detailed information on the study subjects grouped according to critical period of brain development is provided in (Table 1). The results of the hearing tests in all control subjects were normal, and informed written consent was provided by the parents of the infants. With the approval of Tianjin First Central Hospital Medical Ethics Committee (review number: 2018N109KY), our program

Table 1
Groups and group gender composition of the study subjects.

Group		Gender		Sum
		Male	Female	
I	Infants with deafness, 6–24 months	10	7	17
II	Infants with deafness, 24–48 months	9	8	17
III	Control infants, 6–24 months	5	3	8
IV	Control infants, 24–48 months	7	5	12
Sum		31	23	54

Note: p = 0.83 according to Fisher's exact test.

comformed to ethical requirements and can be carried out.

2.2. Execution of the experiment

The subjects could not complete the MRI examination while awake because they were too young; sedation was necessary. Therefore, all subjects completed the MRI examination under sedation with the consent of their parents. After each subject was asleep, he or she was placed supine on a magnetic resonance examination bed. During the scanning process, the subject's head was fixed in place with a headband and a sponge pad to prevent head movement and thereby reduce motion artifacts. The entire experiment involved no task stimuli; the infants simply laid quietly on the bed.

2.3. Magnetic resonance apparatus and imaging method

All subjects underwent MRI scans on a 3.0T MR scanner (Siemens, Trio) with a 16-channel standard quadrature head coil.

The detailed MRI sequence included the following steps. First, all subjects underwent routine whole-brain T1WI and T2WI scans using rapid spin echo (RSE) to exclude central nervous system abnormalities. The parameters were as follows: T1WI: TR/TE = 300/2.5 ms, slice thickness = 4 mm, interlayer spacing = 1.2 mm, matrix = 320 × 320, FOV = 220 × 220 mm, flip angle = 70°, 25 transverse slices covering the whole brain, NEX = 1; T2WI: TR/TE = 6000/93 ms, slice thickness = 4 mm, interlayer spacing = 1.2 mm, matrix = 320 × 320, FOV = 220 × 220 mm, flip angle = 120°, 25 transverse slices covering the whole brain, NEX = 1. Second, gradient recalled echo, echo-planar imaging (GRE-EPI) was performed with the following parameters: TR/TE = 3000 ms/30 ms, FOV = 220 × 220 mm, flip angle = 90°, matrix = 64 × 64, slice thickness = 3 mm, interval 0, 38 transverse slices without gaps covering the whole brain, 230 frames, 8740 total scans, scan time = 660 s. Finally, a whole-brain scan was performed using a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence for 3D reconstruction, spatial registration, and standardization. The parameters were set as follows: TR/TE = 1900/2.53 ms, FOV = 250 × 250 mm, flip angle = 9°, matrix = 256 × 256, slice thickness = 1 mm, interval = 0 mm, 160 sagittal slices without gap covering the whole brain, scan time = 243 s.

2.4. Functional image data processing

2.4.1. Data preprocessing

The raw functional imaging data (Dicom format) were exported to an offline workstation and preprocessed using Statistical Parametric Mapping 8 (SPM8) software, which is recognized internationally for its accuracy. To account for the stability of the machine and the subject's adaptation to the environment, the first 10 time points of the 220 time points of the sedation time series were excluded from analysis. Further preprocessing included slice timing, realignment, normalization, smoothing and removal of linear drift.

2.4.2. ALFF analysis

Using REST software for ALFF analysis, the power spectrum of the signal at 0.01–0.08 Hz was calculated, and the square root was calculated to obtain the low-frequency oscillation amplitude of the signal. Then, the ALFF value of each voxel was divided by the total brain average ALFF value to obtain the normalized ALFF value for each voxel. The normalized ALFF value for each individual was reduced by 1 for within-group and between-group analyses.

2.4.3. Functional connectivity analysis

Using the statistical analysis tools of REST software, two-sample t-tests were performed for comparisons between groups I and III, groups II and IV, groups I and II, and groups III and IV, and the results were displayed using xjview8. Differences between two groups were considered statistically significant at $p < 0.01$ (FDR correction) and cluster size $\geq 270\ mm^3$ (10 voxels).

Functional magnetic resonance data analysis and the processing software REST developed by the National Key Laboratory of Cognitive Neuroscience and Learning of Beijing Normal University were used to delinearize each spatially smoothed image and apply the 0.01–0.08 Hz frequency band to the resulting signal. Filtering to remove interference from high- and low-frequency signals was

Table 2
Comparison of regional ALFF values between groups I and III.

Partition	Voxel	MNI coordinates	*t*
		x, y, z	
Right BA22	15	57, −6, 6	−3.35
Left middle frontal gyrus	71	−33, 39, 30	−2.93
Right middle frontal gyrus	44	48, 42, −6	−3.76
Left superior temporal gyrus	39	−45, 12, −21	−3.06
Right superior temporal gyrus	76	54, 6, −6	−3.27
Right middle temporal gyrus	58	60, −9, −6	−4.31
Right middle frontal gyrus	11	30, 15, 60	3.67
Left superior apex	13	−33, −60, 45	3.08
Right superior apex	41	33, −60, 51	3.02
Right middle occipital gyrus	42	18, −99, 12	3.32

Note: BA denotes Brodmann's area; x, y, and z are Montreal Neurological Institute (MNI) brain map coordinates.

performed. Then, an automated anatomical labeling (AAL) template was used to extract the time series of the 90 regions of each subject's brain, and a 90 × 90 matrix was constructed for each individual. Each element in the matrix was a Person correlation coefficient (r). To improve the normality of distribution of the correlation coefficient values, Fisher transformation (r-to-z) was performed as follows: $z = 0.5 \times \log[(1 + r)/(1-r)]$. A total of 4005 (90 × 89/2) connections, i.e., 4005 z-values, were obtained.

3. Results

3.1. Comparison of ALFF values in different brain areas between groups I and III

Compared to those of the infants in the control group, the ALFF values of the infants in the deafness group were reduced in the right BA22 area, bilateral middle frontal gyrus, bilateral supraorbital gyrus, and right middle temporal gyrus and increased in the right middle frontal gyrus, right middle occipital gyrus, and bilateral superior apex among infants aged 6–24 months (Table 2).

3.2. Comparison of ALFF values in different brain areas between groups II and IV

Compared to those of the infants in the control group, the ALFF values of the infants in the deafness group were reduced in the right BA22 region, bilateral median frontal gyrus, right superior temporal superior gyrus, and left angular gyrus and increased in the left suboccipital gyrus among infants aged 24–48 months (Table 3).

3.3. Identification of areas with ALFF changes between groups I and II

Compared to those of the 6- to 24-month-old infants, the ALFF values of the 24- to 48-month-old infants were reduced in the left BA41, left BA22, left middle frontal gyrus, left inferior frontal gyrus, and left superior temporal gyrus and increased in the bilateral superior apex among infants with deafness (Table 4).

3.4. Identification of areas with ALFF changes between groups III and IV

Compared to those of 6- to 24-month-old control infants, the ALFF values of control 24- to 48-month-old infants were reduced in the bilateral middle frontal gyrus, left inferior frontal gyrus, bilateral superior temporal gyrus, and left middle temporal gyrus (Table 5).

Table 3
Comparison of regional ALFF values between groups II and IV.

Partition	Voxel	MNI coordinates	*t*
		x, y, z	
Right BA22 area	12	60, −10, 7	−3.59
Left middle frontal gyrus	117	−36, 38, 25	−2.89
Right middle frontal gyrus	152	39, 50, 10	−2.78
Right superior temporal gyrus	32	60, 5, −8	−2.71
Left angular gyrus	10	−51, −43, 34	−3.41
Left suboccipital gyrus	10	−18, −94, −5	3.42

Note: BA denotes Brodmann's area; x, y, and z are Montreal Neurological Institute (MNI) brain map coordinates.

Table 4
Comparison of regional ALFF values between groups I and II.

Partition	Voxel	MNI coordinates	*t*
		x, y, z	
Left BA41	10	−51, −25, 10	−2.88
Left BA22	13	−51, −31, 1	−3.10
Left middle frontal gyrus	24	−45, 32, 25	−3.35
Left inferior frontal gyrus	24	−51, 23, −8	−3.08
Left superior temporal gyrus	40	−57, −16, 8	−3.56
Left superior apex	13	−15, −55, 52	2.93
Right superior apex	27	21, −58, 67	3.55

Note: BA denotes Brodmann's area; x, y, and z are Montreal Neurological Institute (MNI) brain map coordinates.

Table 5
Comparison of regional changes in ALFF values between groups III and IV.

Partition	Voxel	MNI coordinates	*t*
		x, y, z	
Left middle frontal gyrus	138	−39, 45, 12	−4.15
Right middle frontal gyrus	90	51, 30, 36	−2.89
Left inferior frontal gyrus	20	−51, 15, 6	−2.92
Left superior temporal gyrus	42	−60, 15, 9	−2.76
Right superior temporal gyrus	16	57, 9, 3	−3.20
Left middle temporal gyrus	57	−54, −51, 15	−3.41

Note: BA denotes Brodmann's area; x, y, and z are Montreal Neurological Institute (MNI) brain map coordinates.

3.5. Comparisons between group I and group III in the resting state: functional connectivity in auditory and language-related brain regions and the whole brain

Compared to that of 6- to 24-month-old control infants, reduced functional connectivity was observed between the right middle frontal gyrus and both the superior frontal gyrus and the lenticular nucleus, the right superior temporal gyrus and the medial frontal gyrus, the left Heschl's gyrus and the right middle temporal gyrus, and the right superior temporal gyrus and the middle temporal gyrus temporal pole in 6- to 24-month-old children with deafness. For the same comparison, increased functional connectivity was observed between the right Heschl's gyrus and the superior frontal gyrus, the medial gyrus, and the angular gyrus; between the left supramarginal gyrus and the inferior occipital gyrus; and between the right Heschl's gyrus and the middle temporal gyrus temporal pole (Tables 6 and 7, Fig. 1).

3.6. Comparisons between groups II and IV in the resting state: functional connectivity in auditory and language-related brain regions and the whole brain

Compared to that of 24- to 48-month-old control infants, reduced functional connectivity was observed between the left inferior frontal gyrus–triangular part and the temporal pole; the left middle temporal gyrus and inferior occipital gyrus; the left supramarginal gyrus and the temporal pole; the right supramarginal gyrus and the bilateral pallidum; the right angular gyrus and the inferior temporal gyrus; and the left Heschl's gyrus and the right middle temporal gyrus in 24- to 48-month-old children with deafness. For the same comparison, increased functional connectivity was observed between the left inferior frontal gyrus–triangular part and the right superior apex; the right middle frontal gyrus and the left inferior frontal gyrus; the orbital part of the left superior temporal gyrus and both the middle temporal gyrus and the right inferior frontal gyrus; and the orbital part of the bilateral angular gyrus and both the left superior temporal gyrus and the right middle temporal gyrus (Tables 8 and 9, Fig. 2).

Table 6
Reduced functional connectivity in group I relative to group III.

Brain region 1	Brain region 2	*Z* (group I)	*Z* (group III)	*P*
MFG.R	SFGdor.R	0.74 ± 0.107	0.90 ± 0.107	0.0017
MFG.R	PUT.R	−0.02 ± 0.147	0.17 ± 0.172	0.0076
STG.R	SFGmed.R	−0.09 ± 0.143	0.18 ± 0.094	0.0043
HES.L	MTG.R	−0.06 ± 0.149	0.13 ± 0.177	0.0096
STG.R	TPOmid.R	0.10 ± 0.206	0.41 ± 0.295	0.0064

Table 7
Increased functional connectivity in group 1 relative to group III.

Brain region 1	Brain region 2	*Z* (group I)	*Z* (group III)	*P*
HES.R	SFGmed.R	−0.23 ± 0.169	0.01 ± 0.150	0.0018
HES.R	ACG.R	−0.12 ± 0.172	0.07 ± 0.138	0.0099
SMG.L	IOG.L	−0.12 ± 0.122	0.07 ± 0.193	0.0073
HES.R	TPOmid.R	−0.23 ± 0.193	−0.02 ± 0.106	0.0093

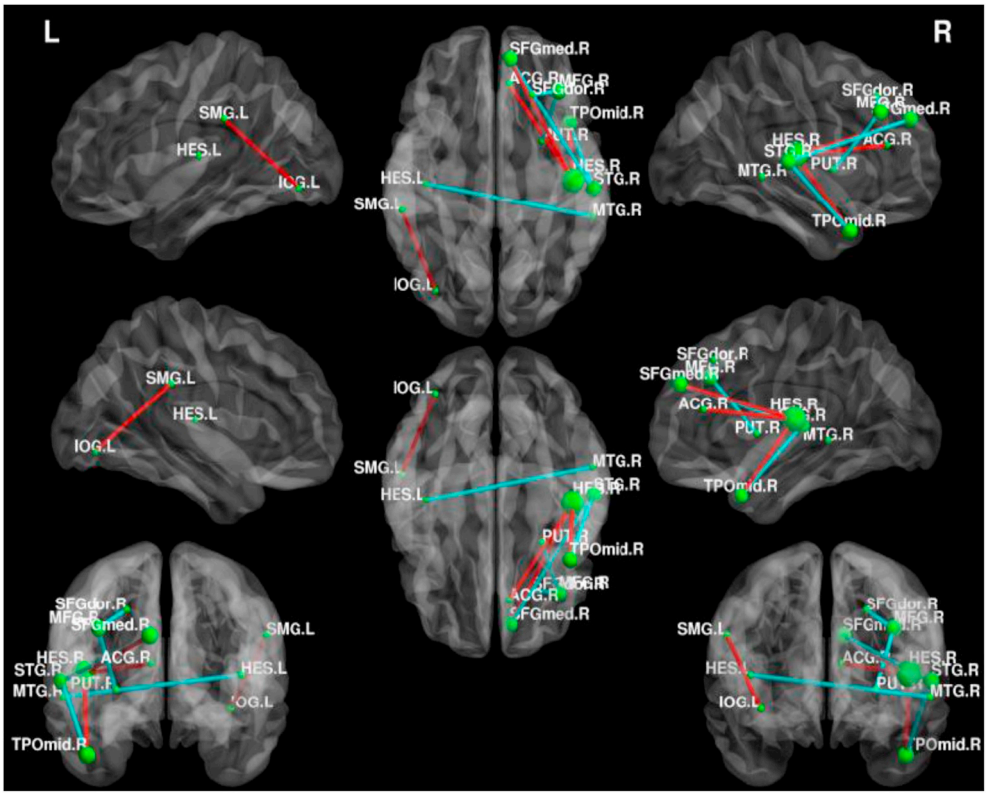

Fig. 1. Enhanced (red line) and reduced (blue line) functional connectivity in group 1 relative to group III. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 8
Reduced functional connectivity in group II relative to group IV.

Brain region 1	Brain region 2	*Z* (group II)	*Z* (group IV)	*P*
IFGtriang.L	TPOsup.L	−0.1 ± 0.241	0.14 ± 0.161	0.0097
MTG.L	IOG.R	0.09 ± 0.147	−0.12 ± 0.174	0.0039
SMG.L	TPOsup.L	−0.1 ± 0.215	0.16 ± 0.156	0.0032
SMG.R	PAL.L	−0.00 ± 0.114	0.10 ± 0.174	0.0067
SMG.R	PAL.R	−0.00 ± 0.124	0.12 ± 0.139	0.0064
ANG.R	ITG.R	0.12 ± 0.243	0.43 ± 0.242	0.0048
HES.L	MTG.R	0.08 ± 0.202	−0.16 ± 0.138	0.0033

3.7. Comparisons between groups I and II in the resting state: functional connectivity in auditory and language-related brain regions and the whole brain

Compared to that of the 6- to 24-month-old infants with deafness, reduced functional connectivity was observed between the bilateral inferior frontal gyrus–triangular part and the right lingual gyrus; the right superior temporal gyrus and the bilateral middle frontal gyrus, the medial bilateral superior frontal gyrus–orbital part and the right lingual gyrus; and the right Heschl's gyrus and the superior apex, the left superior temporal gyrus and the inferior occipital gyrus in 24- to 48-month-old infants with deafness. For the same comparison, increased functional connectivity was observed between the left superior temporal gyrus and the right olfactory

Table 9
Increased functional connectivity in group II relative to group IV.

Brain regions	Brain regions	*Z* (group II)	*Z* (group IV)	*P*
IFGtriang.L	SPG.R	0.16 ± 0.166	−0.12 ± 0.162	0.0002
MTG.R	ORBinf.L	0.22 ± 0.252	−0.06 ± 0.186	0.0065
STG.L	ORBinf.R	0.22 ± 0.229	−0.09 ± 0.199	0.0020
MTG.L	ORBinf.R	0.24 ± 0.158	−0.04 ± 0.159	0.0002
ANG.L	ANG.R	0.77 ± 0.123	0.52 ± 0.194	0.0005
STG.L	MTG.R	0.33 ± 0.230	0.07 ± 0.229	0.0097

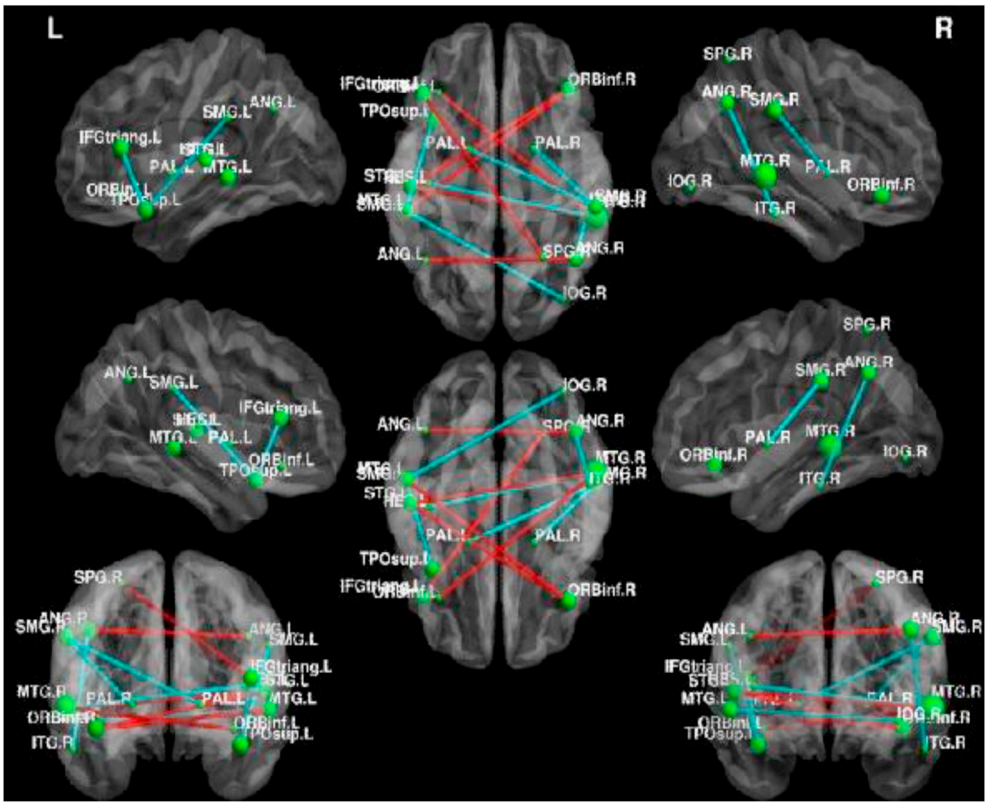

Fig. 2. Enhanced (red line) and reduced (blue line) functional connectivity in group II relative to group IV. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

gyrus; the right Heschl's gyrus and both the left medial superior frontal gyrus and the bilateral inferior frontal gyrus–triangular part; the left superior temporal gyrus and right anterior cingulate gyrus; the bilateral inferior frontal gyrus–triangular part and the inferior occipital gyrus; the right Heschl's gyrus and the postcentral gyrus; the left angular gyrus and the superior apex; and the left Heschl's gyrus and the right supramarginal gyrus (Tables 10 and 11, Fig. 3).

Table 10
Reduced functional connectivity in group II relative to group I.

Brain region 1	Brain region 2	*Z* (group I)	*Z* (group II)	*P*
IFGtriang.L	LING.R	−0.07 ± 0.122	−0.26 ± 0.170	0.0007
IFGtriang.R	LING.R	−0.04 ± 0.187	−0.26 ± 0.209	0.0036
STG.R	SFGmed.L	−0.11 ± 0.168	0.17 ± 0.284	0.0014
STG.R	SFGmed.R	−0.09 ± 0.142	0.22 ± 0.330	0.0011
STG.R	ORBsupmed.L	−0.04 ± 0.230	0.17 ± 0.129	0.0027
STG.R	ORBsupmed.R	−0.02 ± 0.190	0.21 ± 0.157	0.0009
STG.R	LING.R	−0.09 ± 0.158	−0.26 ± 0.153	0.0031
HES.R	SPG.R	−0.03 ± 0.173	−0.21 ± 0.137	0.0022
STG.L	IPL.L	0.02 ± 0.179	−0.19 ± 0.219	0.0058

Table 11
Increased functional connectivity in group II relative to group I.

Brain region 1	Brain region 2	*Z* (group I)	*Z* (group II)	*P*
STG.L	OLF.R	−0.13 ± 0.193	0.09 ± 0.233	0.0072
HES.R	SFGmed.L	−0.26 ± 0.209	−0.04 ± 0.217	0.0046
HES.R	ORBsupmed.L	−0.15 ± 0.172	0.09 ± 0.168	0.0003
HES.R	ORBsupmed.R	−0.16 ± 0.125	0.10 ± 0.217	0.0002
STG.L	ACG.R	−0.12 ± 0.223	0.11 ± 0.175	0.0023
SMG.L	IOG.L	−0.12 ± 0.122	0.03 ± 0.176	0.0091
SMG.R	IOG.L	−0.12 ± 0.138	0.07 ± 0.175	0.0015
HES.R	PoCG.R	0.30 ± 0.238	0.09 ± 0.137	0.0052
ANG.L	SPG.L	0.22 ± 0.209	0.02 ± 0.208	0.0094
HES.L	SMG.R	0.11 ± 0.189	−0.10 ± 0.191	0.0026

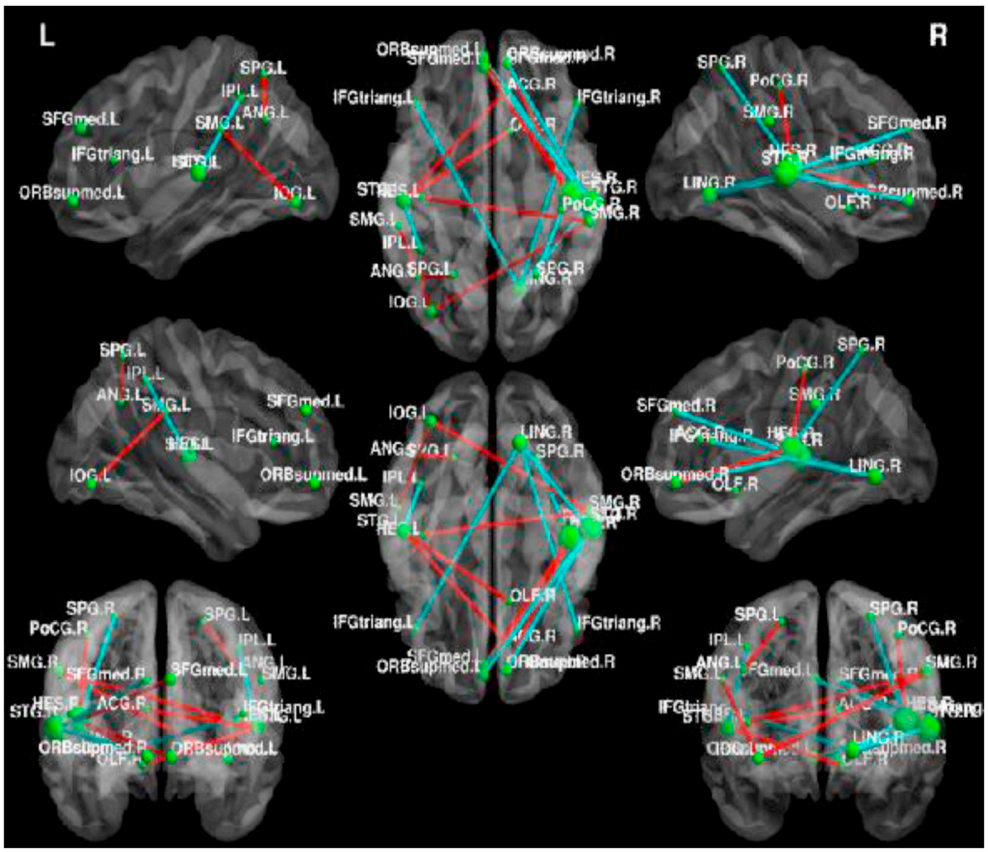

Fig. 3. Enhanced (red line) and reduced (blue line) functional connectivity in group II relative to group III. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.8. Comparisons between groups III and IV in the resting state: functional connectivity in auditory and language-related brain regions and the whole brain

Compared to that of the 6- to 24-month-old control infants, reduced functional connectivity was observed between the following areas in the 24- to 48-month-old control infants: the right middle frontal gyrus and the pallidum; the left inferior frontal gyrus–-triangular part and the precuneus; the right inferior frontal gyrus–triangular part and the left inferior occipital gyrus, the bilateral precuneus, the left lenticular nucleus and the right inferior temporal gyrus; the left angular gyrus and the right cuneus; the left supramarginal gyrus and the precuneus; the right supramarginal gyrus and the left inferior temporal gyrus; and the left Heschl's gyrus and the right middle temporal gyrus (Table 12, Fig. 4).

Table 12
Reduced functional connectivity in group IV relative to group III.

Brain region 1	Brain region 2	*Z* (group III)	*Z* (group IV)	*P*
MFG.R	PAL.L	0.09 ± 0.139	−0.15 ± 0.202	0.0091
IFGtriang.L	PCUN.L	0.09 ± 0.094	−0.29 ± 0.239	0.0038
IFGtriang.R	IPL.L	0.05 ± 0.086	0.32 ± 0.215	0.0033
IFGtriang.R	PCUN.L	−0.05 ± 0.096	−0.29 ± 0.186	0.0034
IFGtriang.R	PCUN.R	0.03 ± 0.098	−0.19 ± 0.161	0.0038
IFGtriang.R	PUT.L	−0.01 ± 0.109	−0.15 ± 0.106	0.0098
IFGtriang.R	ITG.R	−0.07 ± 0.105	0.21 ± 0.226	0.0062
ANG.L	CUN.R	0.01 ± 0.124	−0.24 ± 0.168	0.0032
SMG.L	PCUN.R	0.03 ± 0.159	−0.27 ± 0.227	0.0055
SMG.R	ITG.L	−0.03 ± 0.183	0.23 ± 0.183	0.0095
HES.L	SMG.R	0.13 ± 0.177	−0.16 ± 0.138	0.0012

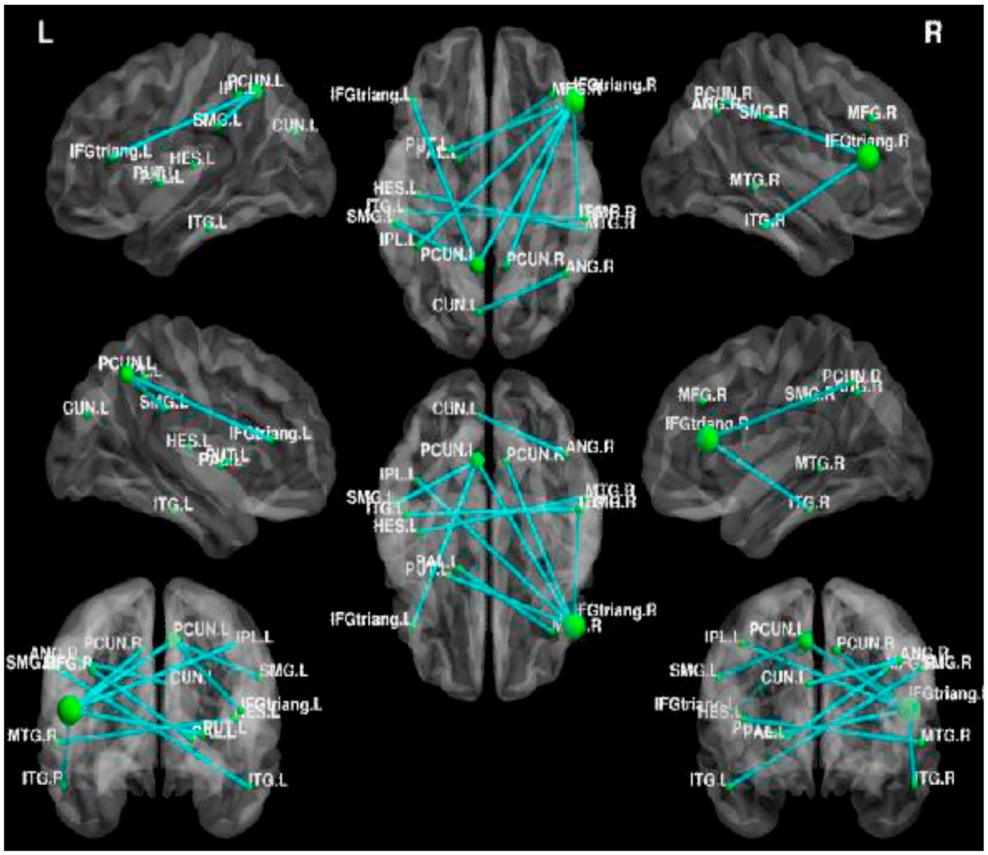

Fig. 4. Reduced (blue line) functional connectivity in group IV relative to group III. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

The purpose of the present study was twofold. First, this study aimed to investigate the changes in ALFF values in auditory and language-related brain regions of infants with congenital extremely severe sensorineural hearing loss aged from 6 to 48 months under sedation to evaluate the functional reorganization of the auditory cortex and language-related brain regions before CI. Second, this study aimed to investigate whether such infants differ from hearing infants in the extent of brain connections between the auditory and language-related brain regions and the whole brain. Lee et al. (2001) found that relative to young normal adults, young pre-lingual patients with hearing loss showed low levels of glucose metabolism in the auditory cortex and related brain areas, which suggest the poor recoverability of auditory cortical function in these patients. Based on the low levels of glucose metabolism in the auditory cortex, it has been inferred that the functions of the auditory cortical brain regions have been replaced with those of other cognitive functional brain regions, contributing to difficulty in recovering cortical function and poor language cognitive abilities (Lee

et al., 2007) The ALFF values in the deafness group and the corresponding control group generally decreased between the ages of 6–24 months and 24–48 months, and the number of brain regions exhibiting reduced ALFF values was higher at 6–24 months than at 24–48 months. These results indicate that the right BA22 region and some language-related brain regions showed low levels of spontaneous neuronal activity in the case of hearing deprivation. Furthermore, the results suggest that the functions of the right BA22 area and some of the language-associated brain regions of infants with deafness aged from 6 to 48 months have not been replaced by those of other brain areas; that is, no significant functional reorganization has occurred. In the right BA22 region, the bilateral middle frontal gyrus and the right superior temporal gyrus, the ALFF values were reduced in infants with deafness relative to those of control infants, suggesting that these brain regions did not undergo functional reorganization during hearing loss lasting 6–48 months. Among infants aged 6–24 months, the ALFF values in the right middle frontal gyrus, middle occipital gyrus, and bilateral superior lobule were increased in the deafness group relative to the those in the control group. Among infants aged 24–48 months, the ALFF values of the left inferior occipital gyrus were increased in the deafness group relative to the control group, possibly due to compensatory effects. Auditory cortical plasticity mainly depends on the duration of hearing deprivation. An electrophysiological study (Ponton et al., 1996) showed that the developmental maturation of the auditory conduction pathway is delayed in infants with hearing loss and manifests as delayed evoked potentials in the P1 auditory cortex. The cross-reorganization of the auditory cortex area (Lambertz, Gizewski, de Greiff, & Forsting, 2005) and the delayed P1 auditory cortical evoked potential (Ponton et al., 1996) are all related to hearing loss duration. In our study, the left BA41, BA22, middle frontal gyrus, inferior frontal gyrus, and superior temporal gyrus showed lower ALFF values in children with deafness at 24–48 months of age than at 6–24 months of age, suggesting that as the duration of hearing loss increases, ALFF values in the left primary and secondary auditory cortex and language-related brain areas gradually increase; i.e., different degrees of functional reorganization occur. Thus, in the left auditory cortex, functional reorganization in language-related brain structures occurred between months 24 and 48. This observation suggests that CI performed after 24 months will affect hearing habilitation differently than CI performed earlier due to the apparent functional reorganization of the auditory and language-related brain regions. The reduced ALFF in regions of the left auditory cortex may reflect a gradual increase in reliance on the left hemisphere during speech development, making the left hemisphere the dominant hemisphere; under these conditions, the right hemisphere is associated with the suppression of language potential.

Comparisons between the results obtained at 6–24 months and at 24–48 months showed that all of the changes in ALFF values in the relevant brain regions at 24–48 months were reductions, suggesting that ALFF values gradually increased in the bilateral middle frontal gyrus, the left inferior frontal gyrus, the middle temporal gyrus and the bilateral superior temporal gyrus, which is consistent with brain development associated with normal hearing. The function of the brain has two basic organizational principles in infants and young children: functional differentiation and functional integration.

In the development of the auditory cortex, the input of external auditory stimuli plays an important role. If appropriate auditory stimuli are not received during the critical period, language and communication obstacles may result. This observation suggests that a lack of hearing will affect the development of hearing and the language center, resulting in a condition known as “deafness and dumbness.” It also indicates that there is a functional connection between the auditory brain area and language-related brain areas. With the extension of hearing loss time, the functional connectivity between different brain regions changes, as demonstrated in this study.

Relative to the corresponding functional connectivity values in the control group, the functional connectivity values of hearing- and language-related brain regions and the whole brain were increased in some locations and decreased in others in the 6- to 24-month-old infants with deafness under sedation. Functional connectivity between the right middle frontal gyrus and the superior temporal gyrus and between the dorsolateral part of the superior frontal gyrus and the medial part of the superior frontal gyrus was reduced in these infants. Some parts of the dorsolateral middle frontal gyrus are associated with complex tissue behavior and highly specific learning and memory functions. It has been speculated that due to hearing loss, the functional connectivity between the language-related brain regions and the frontal lobe is reduced, which in turn affects the acquisition and development of language functions. The functional connectivity between the right middle frontal gyrus and the lenticular nucleus was reduced in the infants with deafness in this study. The lenticular nucleus is an important part of the basal ganglia. The basal ganglia receive incoming signals from brain regions, such as the sensorimotor cortex, the premotor area, and the orbitofrontal cortex. The basal ganglion circuit is transmitted from the projection fibers and then returns from the thalamus to the cerebral cortex to form the cortico-basal ganglia-thalamo-cortical circuit. The functions of general body control, ocular regulation, marginal regulation and prefrontal regulation are subserved by this circuit. The basal ganglia neural circuit mainly consists of two projection systems that regulate extra pyramidal movements directly or indirectly. After applying local cerebral blood flow SPECT imaging to study aphasia, Jodzio, Gasecki, Drumm, Lass, and Nyka (2003) found that subcortical structures played integral roles in speech and language development. In 1997, Nadeau and Crosson described five mechanisms related to aphasia caused by subcortical stroke. One mechanism involves the basal ganglia and other subcortical structures, which are the main components of the reticular system underlying the language structure of the cerebral cortex. Nadeau and Crosson speculated that there is a functional relationship between the basal ganglia area and the language center; if true, this relationship suggests that impairment of the language center may lead to a decrease in functional connectivity between the two regions. The functional connectivity between the left supramarginal gyrus and the inferior occipital gyrus was enhanced in the infants with deafness in this study. The inferior occipital gyrus is the visual center, and the left supramarginal gyrus is the language application center; together, these regions control fine coordination function. A previous study (Lambertz et al., 2005) found that patients with deafness display marked activation in the auditory center in response to visual stimuli, suggesting that in the case of hearing deprivation, reorganization of the auditory cortex and visual cortex occurs. In many cases, such cortical modification allows multisensory cortices to recruit available auditory regions for enhanced visual and/or somatosensory processing at the expense of auditory processing abilities (Kral, 2013; Kral & Sharma, 2012). It can thus be speculated

that hearing deprivation leads to increased functional connectivity between the language center and the visual center.

Compared to the corresponding functional connectivity values of the control group, the functional connectivity values between the language-related brain regions and the temporal pole, inferior occipital gyrus, pallidum and inferior temporal gyrus were reduced in 24- to 48-month-old infants with deafness under sedation. This result suggests a lack of language development under hearing deprivation and consequent reduced functional connectivity with the corresponding brain areas. The functional connectivity between the triangular part of the left inferior frontal gyrus and right superior parietal lobe; the right middle frontal gyrus and the orbital part of left inferior frontal gyrus and the left superior temporal gyrus; and the middle temporal gyrus and the orbital part of right inferior frontal gyrus, the bilateral angular gyrus, the left superior temporal gyrus and the right middle temporal gyrus was reduced. The superior parietal lobe is the somatosensory joint cortex, and the orbital part of the inferior frontal gyrus is associated with logical thinking ability and memory ability, suggesting that hearing loss will increase the connection between auditory language-related brain areas and frontal and parietal functional areas via compensatory effects.

Among the sedated infants with deafness, at 24–48 months relative to 6–24 months, the functional connectivity between the triangular part of the bilateral inferior frontal gyrus and the right lingual gyrus, the right superior temporal gyrus and the medial part of bilateral superior frontal gyrus, and the orbital part of bilateral superior frontal gyrus and the right lingual gyrus was reduced. Furthermore, the functional connectivity between the right Heschl's gyrus and the superior parietal lobe and between the left superior temporal gyrus and inferior occipital gyrus was reduced. The lingual gyrus and suboccipital gyrus are the visual centers, the superior parietal lobe is the somatosensory joint cortex, and the superior frontal gyrus is related to working memory. In the 24- to 48-month-old infants, increased functional connectivity was observed between the left superior temporal gyrus and the right olfactory gyrus; the right Heschl's gyrus and the medial part of left superior frontal gyrus and the orbital part of the bilateral superior frontal gyrus; the left superior temporal gyrus and right anterior cingulate gyrus; the bilateral supramarginal gyrus and inferior occipital gyrus; the right Heschl's gyrus and the postcentral gyrus; the left angular gyrus and the superior parietal lobe; and the left Heschl's gyrus and the right superior occipital gyrus. This finding suggests that loss of neurons due to a complete lack of hearing prevents the normal development of auditory brain regions, thereby hindering the functional connection between the auditory brain regions and the language-related brain regions and impeding the emergence of normal language functions.

In the sedated control infants at 24–48 months of age relative to those at 6–24 months of age, the functional connectivity between auditory and language-related brain regions and the whole brain was universally reduced; that is, as the age of infants with normal hearing increased, brain development gradually occurred, and the functional connectivity between different functional brain regions increased.

In conclusion, our results suggest that CI performed after 24 months may have a weaker effect on the habilitation of hearing and speech functions due to functional reorganization of the auditory and linguistic brain areas over time. Our results suggest that hearing deprivation affects the functional connectivity between both the auditory and language-related brain regions and the corresponding sensory and visual functional brain regions and that this functional connectivity decreases as the duration of hearing loss increases.

Declarations of interest

None.

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