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Altered regional activity and connectivity of functional brain networks in congenital unilateral conductive hearing loss

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ABSTRACT

Neuroimaging studies have shown marked alterations in brain function after auditory deprivation, with these alterations mainly caused by sensorineural hearing loss. To date, however, little is known about the patterns of functional brain reorganization in conductive hearing loss (CHL). The effects of congenital unilateral CHL on human brain were assessed by resting-state functional magnetic resonance imaging in 24 patients with unilateral microtia (UM) and 25 healthy controls. Focal brain function and seed-based functional connectivity were analyzed to characterize spontaneous activity and network changes in UM. Patients with UM showed common alterations in focal brain activities in the left inferior temporal gyrus across different measurements, with these alterations significantly associated with the duration of hearing loss. Additionally, focal brain activities were decreased in the auditory system and increased in the visual system, with a disassociated pattern shown in the default-mode system. Using the left inferior temporal gyrus as the seed region, patients with UM showed lower connectivity with the default-mode system and right visual regions but higher connectivity with the left frontoparietal regions when compared with controls. These results indicate that congenital partial hearing deprivation, despite normal bone conduction hearing, can induce widespread reorganizations that continue into adolescence and adulthood.

1. Introduction

Previous studies have reported alterations in brain function after auditory deprivation, with these alterations mainly caused by sensorineural hearing loss. However, little is known about the patterns of functional brain reorganization in conductive hearing loss (CHL) which results from any barriers that inhibit sound transmission from the external and middle ear to the cochlea. So far, no study has reported functional brain changes based on the etiology of hearing loss.

Sensory deprivation can induce cross-modal neuroplastic changes in sensory cortices (Merabet and Pascual-Leone, 2010). If sensory deprivation occurs early in life, the neural reorganization could become irreversible (Friedmann and Rusou, 2015). Because the development of the auditory cortex is strongly shaped by auditory experience, particularly at an early age (Kilgard et al., 2001), the age of onset of hearing loss is critical for cross-modal reorganization in the brains of deaf individuals (Sadato et al., 2004; Li et al., 2013).

Neuroimaging has revealed widespread changes in brain structure and function of patients with early auditory deprivation. However, the results of studies have been inconsistent. For example, several studies found that gray matter density in the primary auditory cortex was preserved in prelingual deaf adults (Kim et al., 2014; Kumar and Mishra,

Abbreviations: UM, unilateral microtia; NC, normal control; CHL, conductive hearing loss; SNHL, sensorineural hearing loss; PTA, Pure tone audiometry; ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low-frequency fluctuations; ReHo, regional homogeneity; SBFC, seed-based functional connectivity; ROI, region of interest; ITG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPG, inferior parietal gyrus; IFG, inferior frontal gyrus; MNI, Montreal Neurological Institute; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; GSR, global signal regression; nGSR, non-global signal regression.

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2018), whereas others have reported increased gray matter volume in infants (Smith et al., 2011) and decreased gray matter volume in adults (Olulade et al., 2014). Earlier and longer hearing aid use was also found to affect cross-modal reorganization induced by auditory deprivation (Ding et al., 2015). Resting-state functional magnetic resonance imaging (rs-fMRI) showed that the intrinsic functions of different parts of the auditory region were altered in congenitally deaf adults not using hearing aids (Li et al., 2013), whereas connectivity in visual and language regions was altered in prelingually deaf adolescents who had previously used hearing aids (Li et al., 2016). Additionally, anatomic alterations differed in deaf native users of spoken language and deaf native users of sign language, suggesting that cortical plasticity also depends on language experience (Olulade et al., 2014). More recently, neuroimaging showed that tinnitus, a common symptom accompanying hearing loss, can cause functional (Hinkley et al., 2015; Hofmeier et al., 2018) and structural (Besteher et al., 2019) reorganization. Most of the above-mentioned studies, however, did not exclude patients with tinnitus (Sadato et al., 2004; Li et al., 2013; Ding et al., 2015; Li et al., 2016). Therefore, in addition to the differing in analytical methods, these studies recruited subjects from different backgrounds, including differences in developmental stage (infants, adolescents or adults), hearing aid use, language experience (sign or spoken), and symptoms of tinnitus. Taken together, these findings indicate that patterns of brain reorganization may or may not be caused exclusively by early auditory deprivation.

Unilateral deafness is a model of partial auditory deprivation, with total hearing loss on one side but normal hearing on the other side. Although their abilities to localize sounds and recognize speech in the presence of noise are impaired (Sargent et al., 2001), unilaterally deaf individuals are able to communicate well without using sign language or a hearing aid. Brain alterations in unilaterally deaf individuals can therefore be assessed without including the effects of language experience and hearing aid use. Few studies to date have evaluated neuroimaging results in unilaterally deaf persons. Although auditory signals from the hearing ear can reach the auditory cortex (prominently the contralateral cortex), brain reorganizations in subjects with unilateral deafness, occurring in both auditory and non-auditory regions, can be as drastic and widespread as in subjects with bilateral deafness(Schmithorst et al., 2005; Burton et al., 2012; Burton et al., 2013; Pross et al., 2015; Shang et al., 2020). Reorganization differs, however, in unilaterally and bilaterally deaf individuals. For example, postlingual unilateral deafness showed decreased activation in the auditory cortex during visuo-spatial working memory tasks (Qiao et al., 2019), whereas bilateral deafness led to greater activation in the auditory cortex (Ding et al., 2015; Benetti et al., 2017). It remains undetermined, however, whether the plasticity pattern in subjects with postlingual unilateral deafness also occurs in subjects with prelingual unilateral deafness, as there is also a critical developmental period for the auditory cortex in unilaterally deaf individuals (Kral et al., 2013; Tillein et al., 2016).

Microtia is a congenital malformation of the external ear, which can range from minimal structural abnormalities to complete absence of the external ear, accompanied by abnormalities of the middle ear (Luquetti et al., 2011). Atresia is a severe form of microtia, in which the external ear canal is closed or absent and middle ear structures may be missing or abnormally developed. Closure of the external ear canal and malformation of the middle ear can cause severe to profound conductive hearing loss (CHL) on the affected side. In most cases, microtia occurs unilaterally, with a right-side predominance (Harris et al., 1996).

The subjects selected for this study presented with congenital unilateral microtia and unilateral severe CHL, but not sensorineural hearing loss (SNHL), and had no experience with sign language or hearing aid use. In contrast, all previous neuroimaging studies have included patients with SNHL, which was likely accompanied by tinnitus (Jastreboff 1990; Lewis et al., 2020). From our clinical experience, patients with microtia rarely have tinnitus. Moreover, CHL is a milder form of hearing loss than SNHL, with CHL reducing sound transmission only to the cochlea, but having no effect on hearing through bone conduction. Unilateral microtia can therefore model brain reorganization in subjects with congenital partial auditory deprivation.

Rs-fMRI is a promising functional imaging technique that can map regional brain activity and functional connectivity by measuring low-frequency, spontaneous blood oxygen level dependent signals (Biswal et al., 1995). In the past ten years, rs-fMRI has been used to explore experience-related brain development and plasticity. The present study explored brain re-organization in subjects with congenital unilateral CHL by using rs-fMRI to examine both regional activity and the functional connectivity among regions. Specifically, changes in spontaneous neural activity were assessed by calculating the amplitude of low-frequency fluctuations (ALFF) (Zang et al., 2007), fractional amplitude of low-frequency fluctuation (fALFF) (Zou et al., 2008), and regional homogeneity (ReHo) (Zang et al., 2004). Seed-based functional connectivity (SBFC) (Biswal et al., 1995) enabled identification of alterations in the resting-state network that is related to the prior regions. We hypothesized that unilateral CHL at an early age can cause long lasting brain reorganization and that this alteration would correlate with the duration and severity of hearing loss.

2. Materials and methods

2.1. Participants

The present study included 27 patients aged 11–40 years with right-sided congenital unilateral microtia (UM group) and 27 age- and sex-matched normal hearing individuals aged 11–35 years (NC group). Because microtia is usually right-sided and the side of deafness may affect the results of fMRI (Hanss et al., 2009), only subjects with right-sided microtia were included in the present study. All subjects were right-handed. Subjects were excluded if they had known neurologic or psychiatric diseases, brain lesions such as white matter hypoplasia, epilepsy, tumors or strokes, and had contraindications to MR imaging. Patients who had previously received hearing interventions were also excluded. Hearing level was assessed by pure tone audiometry (PTA) in a closed field at six frequencies (0.25, 0.5, 1, 2, 4 and 8 kHz). All subjects in the UM group had severe HL in the affected ear (>60 dB HL), whereas all subjects in the NC group had normal hearing thresholds in both ears (<20 dB HL). Cognitive abilities were evaluated by professionals using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA) test (Nasreddine et al., 2005). Strict quality control was maintained for the integrity of scans, for errors in raw DICOM data, for head motions, and for coverage of the entire brain. Finally, we included 49 participants (24 patients with UM and 25 NCs). The study protocol was approved by the Institutional Ethics Review Board of Peking Union Medical College Hospital, and written informed consent was provided by all subjects prior to their participation.

2.2. fMRI data acquisition

Magnetic resonance images were obtained using a GE750 3.0 T MR scanner with an eight-channel standard quadrature head coil. During the scan, the head of each subject was fixed using foam padding to reduce head movement and earplugs were utilized to minimize machine noise. Subjects were instructed to lie still and relax with their eyes closed but not fall asleep and not think of anything. Functional images were obtained axially with a gradient echo type echo planar imaging (EPI) sequence. The scanning parameters were: a repetition time (TR) of 2000 ms; an echo time (TE) of 30 ms; 36 slices; thickness of 4 mm; gap of 0 mm; 64 × 64 acquisition matrix; flip-angle (FA) of 90°; voxel size of 3.75 × 3.75 × 4 mm^3; and field of view (FOV) of 200 × 200 mm^2. Anatomical images were acquired with a high-resolution T1-weighted gradient-echo sequence and parameters that included a TR of 7.9 ms, a TE of 2.9 ms, an FA of 7°, a thickness of 1 mm, 192 slices, an FOV of 256

× 256 mm^2 and a voxel size of 1 × 1 × 1 mm^3.

2.3. fMRI data pre-processing

All rs-fMRI images were processed using SPM12 (www.fil.ion.ucl.ac.uk/spm/) and SeeCAT (www.nitrc.org/projects/seecat) software. The first 10 time points of the functional imaging were deleted because of the instability of the initial MRI signal and the need for participants to adapt to the scanning environment. Thereafter, slice-timing and head-motion correction were implemented. The corrected images were normalized to the EPI template, resampled to 3-mm isotropic voxels, and further smoothed with a 4-mm full-width at half maximum Gaussian kernel. Confounding signals, including those of white matter and cerebrospinal fluid, as well as linear drift and Friston-24 head-motion parameters, were removed using a linear regression model. The time series for each voxel was temporally band-pass filtered (0.01–0.1 Hz) to reduce low-frequency drift and physiological high-frequency noise. Finally, a scrubbing procedure based on framewise indices was utilized to reduce motion-related effects on FC analysis (Power et al., 2012). Specifically, any volume with a >0.5 mm framewise displacement, as well as its adjacent volumes (two forward and one backward frames) were replaced using linear interpolated data.

2.4. Measurements of resting-state brain function

The amplitude of low-frequency fluctuations (ALFF) was defined as the total power within the frequency range between 0.01 and 0.1 Hz and was considered as an effective indicator of the spontaneous neural activity of specific regions (Zang et al., 2007). The fractional amplitude of low-frequency fluctuation (fALFF) was defined as the division of ALFF within a given frequency band by the whole frequency range for suppressing nonspecific signals in the rs-fMRI data. When compared with ALFF, fALFF was found to be more stable in detecting regional spontaneous neural activity during the resting state by suppressing physiological noise (Zou et al., 2008). Regional homogeneity (ReHo) was defined as the nonparametric concordance of adjacent voxel time series, involving calculations of Kendall's coefficient of concordance (KCC) of the time series of a given voxel with its nearest neighbors (Zang et al., 2004). Thus, increased ReHo indicates a stronger local synchronization of signals with neighboring voxels. Seed-based functional connectivity analysis (SBFC) was performed to determine the functional coordination between a given grey matter voxel and other voxels within the brain (Biswal et al., 1995). Clusters with significant between-group differences in ALFF, fALFF and ReHo were selected as the seed regions to further explore differences in SBFC changes between the UM and NC groups. To calculate the functional connectivity, the average time series of the BOLD signal was extracted from the seed. The temporal correlations between this reference time series and the time courses of all other brain voxels were calculated, and the normality of the data increased by transforming the correlation coefficients to z values using Fisher's r-to-z transformation (Liu et al., 2017). A mask generated by thresholding the gray matter probability map in SPM 12 at 0.2 was applied across all analyses. Voxels that were not covered by the individuals' data were removed.

2.5. Global signal regression

The global signal is a "catch-all" signal that reflects the contributions of a variety of noise components, including both neuronal components and physical confounders such as respiration and movement (Liu et al., 2017; Murphy and Fox 2017). Global signal regression (GSR) uses linear regression to remove the global signal from the time series of each voxel (Macey et al., 2004). It is unclear, however, whether GSR should be used in the preprocessing of rs-fMRI data. To examine the effect of GSR on UM-related functional alterations, rs-fMRI data were analyzed both with and without GSR during preprocessing.

2.6. Statistical analysis

Clinical data were analyzed using SPSS 18.0 software. Functional data were analyzed using a statistical module in SPM12. Categorical data in the two groups were compared using Fisher's exact test, whereas continuous data were compared using two-sample t-tests. ALFF, fALFF, ReHo and SBFC were compared in the two groups with regressing covariates such as age, gender and educational level. Gaussian random field (GRF) corrections were used for multiple comparisons ($p < 0.001$ at the voxel level and $p < 0.05$ at the cluster level), with the results shown using BrainNet Viewer (www.nitrc.org/projects/bnv/) (Xia et al., 2013). ROI-wise Pearson's correlation analysis was used to investigate the relationship between brain regions showing group differences and clinical features. Statistical significance was defined as a threshold $p < 0.05$ with the Bonferroni correction.

3. Results

3.1. Demographic and clinical characteristics

A comparison of the clinical and demographic characteristics showed no significant between-group differences in gender, age or educational level (Table 1). The mean threshold of pure tone audiometry (PTA) of the affected ear differed significantly in the two groups ($p < 0.001$), but the cognitive scores (MMSE and MoCA) did not differ significantly in the UM and control groups.

3.2. Differences in regional activity and connectivity

Between-group difference maps of each measurement (without thresholding) are shown in Supplemental Fig. 1. Multiple comparison corrections (cluster-level corrected $P < 0.05$ and voxel-level corrected $P < 0.001$) were performed to further reveal differences in functional brain measurements between the UM and NC groups. Compared with controls, patients with UM had lower ALFF values in the left temporal pole, superior temporal gyrus, middle temporal gyrus, and medial prefrontal cortex; and higher ALFF values in the left inferior temporal gyrus and precuneus. In addition, the UM group had higher fALFF values in the left inferior temporal gyrus and fusiform and higher ReHo values in the left inferior temporal gyrus. Notably, ALFF, fALFF, and ReHo measurements showed convergent alterations in the left inferior temporal gyrus, with this region regarded as the seed for SBFC analysis. Compared with controls, subjects in the UM group showed lower connectivity with the left precuneus, right fusiform and right cuneus and higher connectivity with the left inferior parietal gyrus and inferior frontal gyrus (Fig. 1, Table 2).

Table 1
Demographic and clinical characteristics of the study subjects.

	UM (n = 24)	NC (n = 25)	p value
Age (years)	18.6 ± 6.6	19.5 ± 4.3	0.55
Gender (male/female)	17/8	18/8	0.92
Education level (years)	13.5 ± 3.6	13.9 ± 3.2	0.35
Deafness side	Right	–	–
Handedness (right/left)	24/0	25/0	1.00
Disease duration (year)	18.6 ± 6.6	–	–
PTA of affected ear (dB HL)	75.4 ± 4.8	15.1 ± 2.3 [a]	<0.001
MMSE	28.1 ± 0.8	28.4 ± 0.7	0.19
MoCA	28.3 ± 0.9	28.6 ± 0.8	0.23

Data were presented as mean ± standard deviation or number.
UM, unilateral microtia; NC, normal control; PTA, pure tone audiometry; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment Scale.
[a]PTA for NC refers to that of the worse ear.

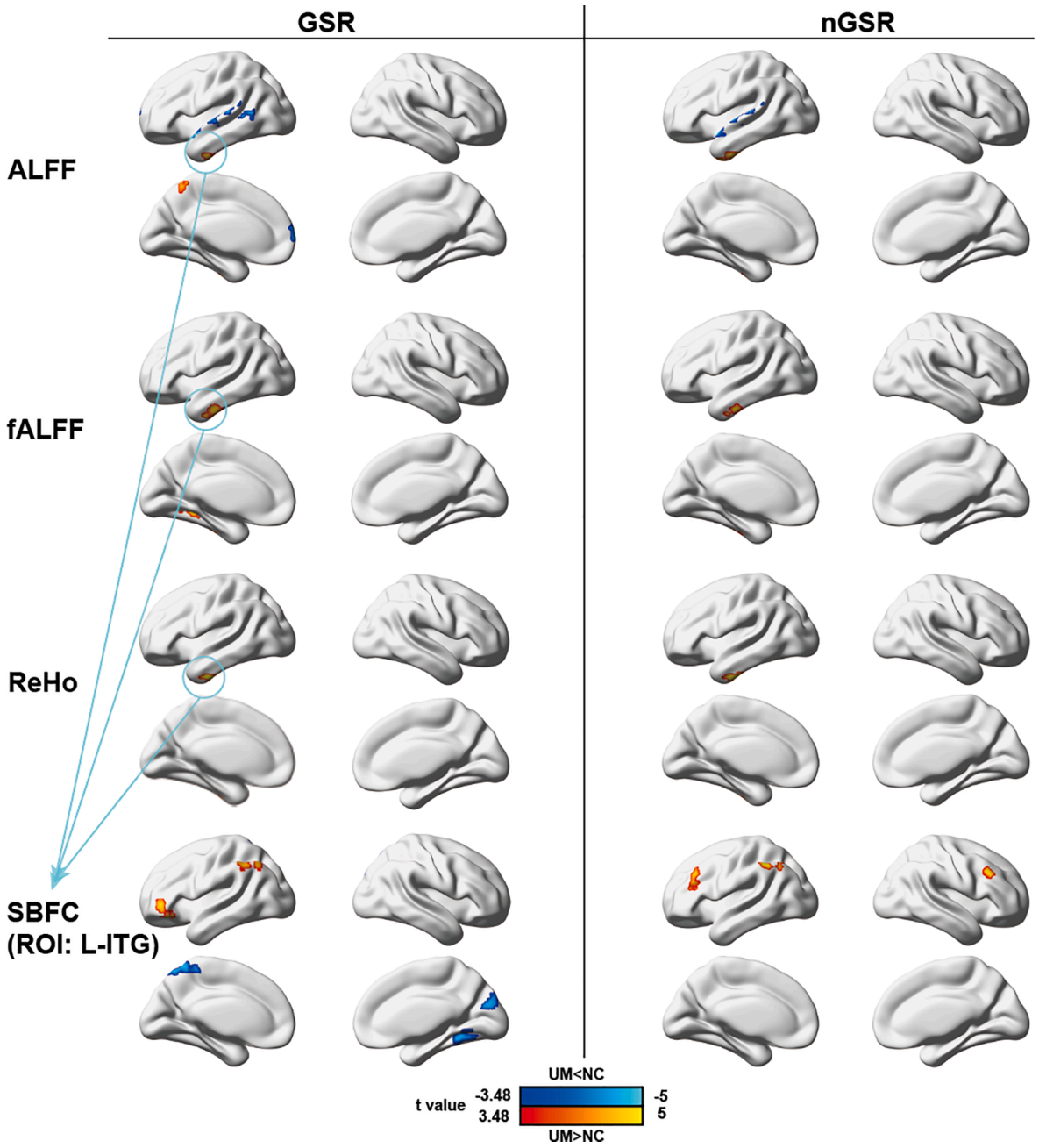

Fig. 1. Significant clusters showing differences in metrics between patients with unilateral microtia (UM) and normal controls (NC) with and without GSR. Thresholds were set at $p < 0.001$ at the voxel level and $p < 0.05$ after Gaussian random field correction. GSR, global signal regression; nGSR, non-global signal regression; ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low-frequency fluctuations; ReHo, regional homogeneity; SBFC, seed-based functional connectivity; R, right sided; L, left sided; ITG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPG, inferior parietal gyrus; IFG, inferior frontal gyrus; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; UM, unilateral microtia; NC, normal control.

3.3. GSR effects on between-group differences

The results obtained without using GSR were generally consistent with those using GSR (Fig. 1). However, the GSR strategy had an impact in several specific regions. Specifically, reproducible alterations of regional activity in the left superior temporal gyrus and inferior temporal gyrus were shown in the UM group in both GSR and nGSR data. Alterations in these regions have been reported in previous neuroimaging studies of hearing loss (Hanss et al., 2009; Schmithorst et al., 2014). However, the GSR effects were more obvious in SBFC analysis, with 2 regions (the left inferior parietal gyrus and inferior frontal gyrus) showing increased FC that were replicated with nGSR data but more regions (the right fusiform, cuneus and the left precuneus) showing decreased FC (Tables 2, 3).

3.4. Associations with clinical variables

To determine if clinical variables were associated with the functional brain measurements, we assessed correlations of hearing threshold, duration of hearing loss, MMSE, and MoCA scores with functional brain measurements that differed significantly in the two groups. The Bonferroni correction for multiple comparisons was applied ($P < 0.05$ were considered statistically significant). The duration of disease in the UM group showed significant positive correlations with the ALFF ($p =$

Table 2
Clusters with significant group effects in data with GSR.

Metric	direction	regions	Voxels	MNI coordinates			t value
				x	y	z	
ALFF	UM > NC	L.ITG, BA20	79	−45	−12	−42	4.65
		L.Precuneus, BA5	91	−12	−57	51	4.41
	UM < NC	L.Temporal pole, BA21	69	−63	6	−9	−4.22
		L.STG, BA22/42	173	−54	−18	0	−4.95
		L.MTG, BA21	84	−54	−54	6	−4.77
		L.vmPFC, BA10	71	−3	63	6	−4.16
fALFF	UM > NC	L.ITG, BA20	104	−51	−15	−30	4.85
		L.Fusiform, BA37	60	−33	−48	−6	4.77
ReHo	UM > NC	L.ITG, BA20	83	−48	−15	−39	5.23
SBFC	UM > NC	L.IPG, BA40	163	−57	−45	48	4.32
(Seed: L. ITG)		L.IFG, BA45	181	−42	42	0	5.17
	UM < NC	R.Fusiform, BA37	145	24	−57	−15	−5.05
		R.Cuneus, BA18	141	3	−84	24	−4.98
		L.Precuneus, BA5	135	−12	−54	63	−5.25

R, right sided; L, left sided; MNI, Montreal Neurological Institute. ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low-frequency fluctuations; ReHo, regional homogeneity; SBFC, seed-based functional connectivity; ROI, region of interest; ITG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPG, inferior parietal gyrus; IFG, inferior frontal gyrus.

Table 3
Clusters with significant group effects in data without GSR.

Metric	Direction	Regions	Voxels	MNI coordinates			t value
				x	y	z	
ALFF	UM > NC	L.ITG, BA20	86	−54	−6	−39	4.72
	UM < NC	L.Temporal pole, BA21	71	−63	6	−9	−4.57
		L.STG, BA22/42	131	−66	−6	3	−4.81
fALFF	UM > NC	L.ITG, BA20	91	−31	−15	−30	4.80
ReHo	UM > NC	L.ITG, BA20	84	−37	−15	−39	4.69
SBFC	UM > NC	L.IPG, BA40	105	−57	−45	48	5.21
(Seed: L. ITG)		L.IFG, BA45	117	−39	30	30	4.56
		R.IFG, BA44	95	39	21	33	5.14

0.021) and fALFF ($p = 0.011$) values of the left inferior temporal gyrus and tended to correlated with increased ReHo values in the left inferior temporal gyrus ($p = 0.061$, Supplemental Table 1). Additionally, the ALFF value of the left inferior temporal gyrus correlated negatively with hearing threshold ($p < 0.001$). No correlation was found between altered SBFC and clinical variables (Fig. 2, Supplemental Table 1).

4. Discussion

Using UM as a research model, this study is the first to assess the effects of congenital unilateral CHL on brain organization using rs-fMRI. The present study demonstrated that the UM group had alterations in regional activity and functional connectivity in sensory processing networks, including the auditory and visual cortices. Regional activity in the left inferior temporal gyrus was abnormally high in the UM group, with these increases being positively correlated with the duration of hearing loss. In addition, we observed the involvement of frontoparietal regions in functional reorganization and the dissociated pattern of functional connectivity between the default mode and sensory processing networks. These findings enhance our knowledge of the functional network reconfiguration in patients with congenital CHL, showing that this reconfiguration involves both low-level sensory processing networks and high-order cognitive networks. The results indicate that partial hearing deprivation with normal bone conduction hearing can still cause functional reorganization, which continues into adolescence and adulthood.

4.1. Plasticity in the auditory network

The human brain has a remarkable ability to reorganize itself when deprived of a sensory modality. Intra-modal plasticity refers to brain changes that are induced within a particular region as a result of decreased input into that sensory system. The superior part of the superior temporal gyrus includes both the primary and secondary auditory sensory cortices (the Heschl gyrus and planum temporale). Spontaneous regional brain activities (ALFF and ReHo) of auditory regions were found to be lower in infants with congenital SNHL than in normal hearing subjects (Xia et al., 2017). Moreover, the gray matter volume of the left superior temporal gyrus was found to be lower in patients with right-sided SNHL (Yang et al., 2014). We expected that most alterations in patients with UM would occur in other brain regions, but not in the auditory network per se, as the latter had never been completely deprived of its natural input (i.e., normal bone conduction hearing). However, we found that ALFF values were decreased in the superior temporal gyrus and temporal pole. This finding lead to the assumption that partial auditory deprivation, even a mild form of hearing loss such as CHL, can cause reorganization in the auditory cortex. We found that the ALFF value of the left superior temporal gyrus correlated with disease severity (hearing threshold), suggesting a mechanism involving disuse and atrophy. However, our result is incompatible with the previous finding that patients with right-sided SNHL showed higher fALFF values in left Heschl's gyrus and superior temporal gyrus (Zhu et al., 2020), which may be explained by that our study included congenital hearing loss whereas the previous study included post-lingual hearing loss. Besides, methodological differences, including regional activity measurements and head-motion processing, might be another reason. In this study, the plasticity of the auditory network mainly occurred in the left hemisphere, as the auditory cortex displays lateralization asymmetries and all the subjects had right-sided microtia. A previous study proposed that left hemispherical auditory regions were more resilient than right hemispherical auditory regions to reduced auditory stimulation from the deaf right ear (Burton et al., 2012). It would be interesting to determine whether patients with left-sided microtia present with more drastic neural plasticity.

4.2. Cross-modal plasticity

Cross-modal plasticity can be a result of sensory deprivation, whereby cortical regions of the deprived modality may be recruited by the remaining, intact sensory modalities. Cross-modal plasticity in deaf patients, especially audiovisual plasticity, has been observed in both task-based and resting-state fMRI studies, with the auditory cortex recruited for visual processing (Glick and Sharma, 2017). However, audiovisual plasticity can manifest differently, with visual networks showing less involvement in audiovisual processing. Compared with controls, children with unilateral SNHL showed lower activation of secondary visual processing regions during audiovisual tasks (Schmithorst et al., 2014) and a study using resting-state fMRI showed decreased functional connectivity between the primary auditory cortex

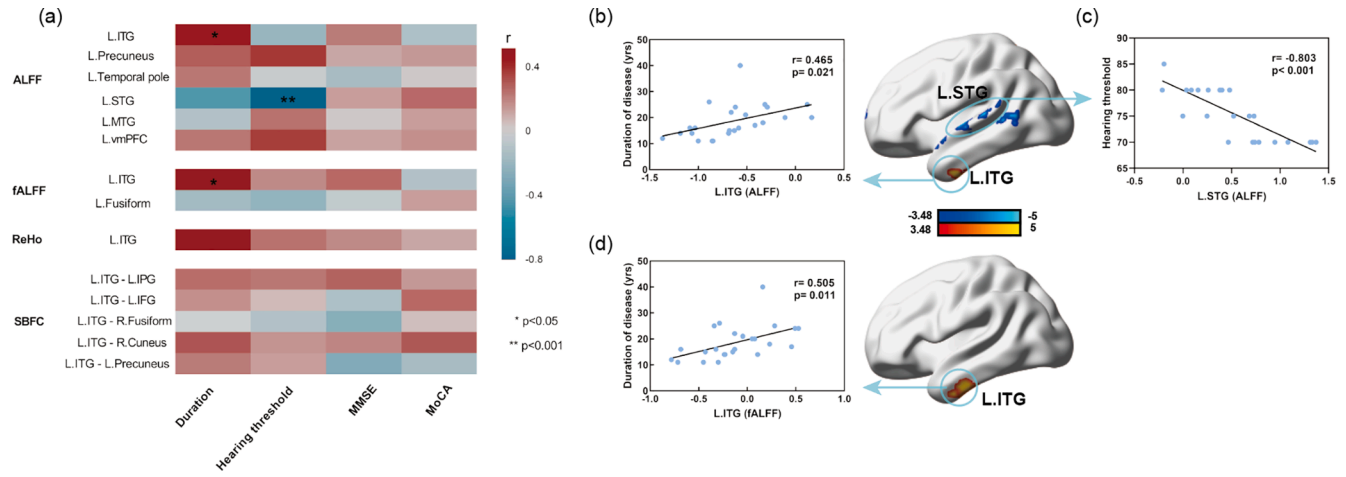

Fig. 2. Relationships between fMRI measurements and clinical variables. (a) Correlation coefficients between fMRI metrics and clinical variables. Red indicates positive coefficients, blue indicates negative coefficients; (b) Positive correlation between disease duration and ALFF of L.ITG ($r = 0.465$, $p = 0.021$); (c) Negative correlation between hearing threshold and ALFF of L.STG ($r = –0.803$, $p < 0.001$); (d) Positive correlation between disease duration and fALFF of L.ITG ($r = 0.505$, $p < 0.001$). ALFF, amplitude of low-frequency fluctuations; fALFF, fractional amplitude of low-frequency fluctuations; ReHo, regional homogeneity; SBFC, seed-based functional connectivity; R, right sided; L, left sided; ITG, inferior temporal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; IPG, inferior parietal gyrus; IFG, inferior frontal gyrus; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

and the visual cortex in adults with unilateral SNHL (Liu et al., 2015). Similar results were observed in the present study. The inferior temporal gyrus is involved in visual recognition memory, semantic processing and audiovisual integration (Binder et al., 2000). Our study found that ALFF/fALFF/ReHo values within the left inferior temporal gyrus were greater in the UM than in the NC group, with or without GSR, consistent with findings in patients with unilateral SNHL (Yang et al., 2014). This result may reflect enhanced audiovisual integration in patients with UM.

The fusiform cortex is part of the ventral visual stream and is associated with face processing (Kanwisher et al., 1997). Although fALFF values in the left inferior temporal gyrus and left fusiform were higher in UM patients, this group also showed decreased FC between the left inferior temporal gyrus and the right fusiform and cuneus. These could be related to fewer resources of the audiovisual integration cortices allocated to visual cortices of the contralateral hemisphere in a resting state, with more resources allocated to enhance ipsilateral audiovisual processing. Interestingly, the intermediate region of the left middle temporal gyrus, which was found to be sensitive to words and emblems (Papeo et al., 2019), demonstrated lower ALFF values in the UM group. This finding suggests that audiovisual plasticity may be region-specific, as different regions of visual processing (fusiform and middle temporal gyrus) differ in spontaneous regional activity in the resting state. Further task-based fMRI studies and more detailed cognitive tests are needed to explore the mechanism underlying this phenomenon.

Notably, we found that increased ALFF/fALFF values within the left inferior temporal gyrus were significantly correlated with disease duration, with the correlation between ReHo and duration in this region being nearly significant. This gives us a hint that each of the spontaneous regional activity measurements may be useful to characterize HL-related neural effects. The inferior temporal gyrus may be a special hub that is more sensitive than the auditory cortex under conditions of chronic hearing deprivation, with the abnormally high spontaneous regional activity in this region resulting from adaptive and compensatory processes (Bavelier et al., 2001). Our funding indicates that the inferior temporal gyrus plays an important role in the baseline brain function of UM patients and may be a potential imaging marker that mirrors the neurological effects associated with hearing loss. Studies assessing whether alterations in the inferior temporal gyrus are reversible after rehabilitation would be of interest.

4.3. *Reorganization in higher-order networks*

Sensory processing is under the top-down control of the frontal and parietal regions associated with sensory attention (Ruff, 2013). Importantly, higher-order cognitive networks might participate in attentional transitions from the impaired to the retained sensory cortex during cross-modal plasticity. SNHL was found to involve abnormal functional coupling among networks involved in sensory attention control (e.g., the frontoparietal and dorsal attention networks) (Luan et al., 2019). In the present study, the left inferior frontal gyrus and the inferior parietal gyrus showed increased FC with the seed region (i.e., the left inferior temporal gyrus) in the UM group. The inferior frontal gyrus is involved in temporal activities, particularly sound discrimination and language processing (Belin et al., 2002), with the inferior parietal lobe functionally contributing to social cognition and language (Bzdok et al., 2016). It is likely that hearing deprivation results in dysfunctional top-down control of multiple sensory processing pathways.

Neuropsychological studies have also shown that hearing deprivation has adverse impacts on attention (Guerreiro and Van Gerven, 2017), memory (Smith and Pichora-Fuller, 2015), executive control (Lin et al., 2011), and language (Halliday et al., 2017). Hearing loss has also been associated with dementia (Gurgel et al., 2014). The default mode network (DMN) plays an important role in self-referential mental processing (e.g., episodic memory and social cognitive processes) (Leech and Sharp, 2014). Abnormal activity and functional connectivity within the DMN have been observed in patients with hearing loss, indicating that the DMN may be susceptible to chronic auditory deprivation and may be associated with cognitive deficits. Functionally, the DMN can be divided into two major subdivisions: the anterior DNM (aDMN), associated with self-referential mental activity; and the posterior DMN (pDMN), associated with both consciousness and recollection of prior experiences (Raichle, 2015). The functional balance between the aDMN and pDMN is important for normal cognition and emotion processing. Compared with normal controls, the UM group presented with decreased ALFF in the left medial prefrontal cortex (a core structure of the aDMN) and increased ALFF in the left precuneus (a key region of the pDMN). Functional imaging has shown that the DMN participates in perceptual processing by retrieving information from memory (González-García et al., 2018). During this memory retrieval task, the pDMN is significantly activated, whereas the medial prefrontal cortex (aDMN) is deactivated (Sestieri et al., 2011). These findings suggest that

increased ALLF in the precuneus may be a compensatory response to enhance perceptual processing, whereas the ALFF in the medial prefrontal cortex is decreased to reach a balance. However, we also noticed decreased FC between the left inferior temporal gyrus and the left precuneus in the UM group, indicating a dissociation pattern of FC between the DMN and the sensory processing network. Although abnormal neurological changes were observed in higher-order networks, no significant differences in MMSE and MoCA were observed between the UM and NC groups. However, both MMSE and MoCA are relatively insensitive to mild/early cognitive disorders. This limitation may be overcome by other tests, such as auditory verbal learning and symbol digit modalities tests.

4.4. The effects of GSR on the reproducibility of functional alterations

The global signal is defined as the mean time course computed over all voxels within the brain (Liu et al., 2017). GSR removes the whole-brain average signal from each individual voxel by using linear regression, which is thought to improve the anatomical specificity of functional-connectivity measures and to reduce motion-related confounders in functional-connectivity analyses (Aquino et al., 2020). However, the usefulness of GSR in the analysis of rs-fMRI results remains unclear because the global signal contains the underlying neural activity (Scholvinck et al., 2010), as well as non-physiological and physiological confounders, such as head motion and cardiac and respiratory cycles (Liu et al., 2017). Therefore, there is great concern that GSR may remove information of interest, as well as altering resting state measurements such as ReHo (Zuo et al., 2013) and functional connectivity (Chai et al., 2012). However, no previous rs-fMRI studies in subjects with hearing loss have investigated the effects of GSR, and most did not mention its use. In our study, between-group differences in local measurements (i.e., ALFF, fALFF and ReHo) did not differ in data with and without GSR, whereas GSR enhanced the ability to detect alterations in SBFC. Because GSR introduces negative correlations (Murphy et al., 2009; Chai et al., 2012) and reduces resting-state FC strength (Li et al., 2019), our finding, that several regions had decreased FC under GSR, was not surprising. Care should be exercised in interpreting these results, however, as they might be a mathematical consequence of GSR. Future studies utilizing noise correction methods other than GSR, such as component based noise reduction (CompCor) (Behzadi et al., 2007), would be valuable.

4.5. Limitations

This study had several limitations. First, the sample size was relatively small, which may have caused selection bias, suggesting the need to verify these in a larger sample. Second, to increase the homogeneity of participants, this study only included patients with right-side microtia. Future studies should therefore include patients with left-side microtia, thereby improving the generalization of the results. Third, the sample included a large age range from 11 to 40 years, with nearly one-third in their early adolescence, where potential development effects could be involved. Forth, this study shows relatively few results from the large number of potential correlations analyzed between fMRI metrics and clinical correlates. The significance of these results was corrected for multiple comparisons. Nonetheless, the generalizability of these results needs to be further examined in the future. Fifth, the inclusion of MMSE and MoCA in the correlation analyses may introduce bias, due to their insensitivity, or due to that UM patients could be cognitively normal. Further studies with more specific tests are needed to identify cognitive deficits and their correlation with fMRI metrics in UM patients. Finally, this study could not further analyze and discuss the specific role of each alteration and its contributions to sensory or cognitive function in patients with UM. Studies are needed to assess the specific mechanisms underlying these findings.

5. Conclusion

The present study showed that regional activity and functional connectivity in sensory processing networks and higher-order cognitive networks were altered in patients with UM (i.e., congenital unilateral CHL) compared with controls. Alterations in these regions suggest cross-modal plasticity involving the auditory and visual cortices, as well as the involvement of frontoparietal regions in functional reorganization and the dissociated pattern of functional connectivity between the default mode and sensory processing networks. These findings may provide insight into the mechanism by which unilateral auditory deprivation at an early age affects brain development and improve our understanding of the impact of CHL on brain plasticity.

6. Declarations

Ethics approval and consent to participate: This retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital (reference number: JS-796).

CRediT authorship contribution statement

Tengyu Yang: Formal analysis, Methodology, Methodology, Software, Writing - original draft, Validation. **Qiang Liu:** Data curation, Software, Resources. **Xinmiao Fan:** Software, Data curation, Investigation. **Bo Hou:** Resources, Data curation, Methodology, Supervision. **Jian Wang:** Resources, Supervision, Validation. **Xiaowei Chen:** Conceptualization, Writing - review & editing, Funding acquisition, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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