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Research article

Convergent and divergent functional connectivity patterns in patients with long-term left-sided and right-sided deafness

Yanyang Zhang[a], Zhiqi Mao[a,1], Shiyu Feng[a], Wenxin Wang[a,b], Jun Zhang[a], Xinguang Yu[a,*]

[a] Department of Neurosurgery, PLA General Hospital, Beijing, 100853, China
[b] Department of Radiology, PLA General Hospital, Beijing, 100853, China

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ABSTRACT

Cortical reorganization may be induced in long-term single-sided deafness (SD); however, the influence of the deafness side on the functional changes remains poorly understood. Here, we investigated whole-brain functional connectivity patterns in long-term SD patients. The normalized voxel-based functional connectivity strength (FCS) was determined using resting-state fMRI (rs-fMRI) in 17 left-sided deafness (LD) patients, 21 right-sided deafness (RD) patients and 21 healthy controls (HCs). Relative to the HCs, both the LD and RD patients exhibited a reduction in the FCS in the ipsilateral visual cortex. However, compared to that in the HCs, a significantly higher FCS was observed in some regions in the salience and default-mode networks in the RD patients, but this FCS alternation pattern was not observed in the LD patients. A direct comparison of the two patient groups revealed a significantly increased FCS in the supplemental motor area in the LD group. Altogether, the long-term SD groups with LD and RD exhibited convergent and divergent functional connectivity patterns in whole-brain networks, providing promising evidence that the functional changes in long-term SD are highly deafness-side-dependent.

1. Introduction

Single-sided deafness (SD) is frequent in newborns (0.5/1000 newborns) [35,37], and the incidence increases with age [32]. SD can be caused by a variety of insults, particularly otologic disease, degeneration, trauma and congenital anomalies [7]. This imbalanced auditory input causes difficulties in directional hearing, multi-speaker identification, and signal extraction in noise [23].

In normally-hearing subjects, the contralateral projection pathway is dominant both anatomically and functionally [7]. In SD patients, due to the monaural auditory input, plastic reorganizations often occur in the hemisphere contralateral to the hearing ear [20]. Thus, the deafness side likely has an appreciable impact on the patterns of plastic reorganizations, which are due to the hemispheric asymmetries. While the cortical reorganization in SD has been verified, only a few studies have investigated the influence of the deafness side on the reorganization. Some studies [16,30,38,39] found distinctly different patterns of cortical reorganization between left-sided deafness (LD) and right-sided deafness (RD), whereas other studies [34] found no difference. Furthermore, most studies primarily focused on the SD-associated asymmetrical task-related activation within the auditory cortex. Importantly, recent studies have expanded upon the simplistic mapping of the auditory cortex by emphasizing the conjoint function of brain areas acting together as large-scale networks [5,21]. However, from the network perspective, the influence of the deafness side on the functional changes in the brain in SD remains poorly understood.

Resting-state MRI (rs-fMRI) is a non-invasive measure of spontaneous brain activity and has the potential to assess the inter-region/voxel functional connectivity (FC), which is represented by a correlation of time series fluctuations [15,25]. The examination of this physiological connectivity offers new insight into the intrinsic connectivity in the human brain [6]. To the best of our knowledge, very few rs-fMRI studies involving SD patients have been reported to date. Using regional homogeneity (ReHo) measurements, Wang et al. [34] demonstrated a shared reduction in the ReHo in the visual cortex in LD and RD patients. Using a seed-based analysis, Zhang et al. [38] detected changes in the connectivity in the default-mode network (DMN), and these changes depended on the deafness side. However, the ReHo reflects the synchronization of time courses between neighboring regions, and seed-based approaches only focus on brain connectivity within specific seed-

Abbreviations: ACC, anterior cingulate cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; FCS, functional connectivity strength; GSR, global signal regression; LD, left-sided deafness; RD, right-sided deafness; ROL, rolandic operculum; SD, single-sided deafness; SMA, supplemental motor area

* Corresponding author.
E-mail address: yuxinguang_301@163.com (X. Yu).
[1] This author contributed equally.

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associated subnetworks. An examination of the whole-brain FC pattern using a data-driven approach has not been performed in UHL.

Here, we used rs-fMRI and voxel-based analyses to comprehensively investigate the whole-brain FC patterns in SD patients. This voxel-wise approach avoids the parcellation-dependent effects on the topological properties of brain networks [11,31]. Because of the abnormal sensory input in both LD and RD patients, we hypothesize that these two groups would show common changes in the FC in primary sensory areas. More importantly, because previous studies have shown differential brain plasticity between LD and RD patients, we hypothesize that these two patient groups show disparate functional connectivity patterns in specific neuronal circuitry.

2. Materials and methods

2.1. Patients

Thirty-eight long-term SD patients with primary ipsilateral acoustic neuroma (AN) were included in this study. Specifically, 17 patients had long-term LD, and 21 patients had long-term RD without tinnitus. In addition, we selected 21 age- and sex-matched healthy controls (HCs). The pure tone average (PTA) was measured by pure tone audiometry using seven different octave frequencies (0.125, 0.25, 0.5, 1, 2, 4 and 8 kHz) to detect the hearing level. All patients in this study were post-lingual SD patients with a hearing deficit in the affected ear (PTA $\geq$ 40 dB) and normal hearing in the unaffected ear (PTA $\leq$ 20 dB). The control subjects had a PTA below 20 dB in both ears. All participants were right-handed. The study was approved by the local ethics committee of the Chinese People's Liberation Army (PLA) General Hospital, and written informed consent was obtained from each participant.

2.2. Image acquisition and preprocessing

All subjects underwent T1-weighted and rs-fMRI scans using a GE750 3.0 T scanner with an 8-channel head coil. During the scan, the subjects were instructed to relax with their eyes closed but not to fall asleep. All rs-fMRI images were preprocessed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) [8], and the preprocessing included the removal of the first 10 time points, slice-timing, realignment, spatial normalization, line detrending, nuisance covariates regression and band-pass filtering. Because the global signal regression (GSR) could introduce spurious anti-correlations between brain regions [28], we reanalyzed the data without GSR to examine whether the process of GSR affected our results. For details regarding the scanning parameters and image preprocessing, see Supplement Materials.

2.3. Whole-brain functional connectivity strength (FCS) analysis

Briefly, for each participant, we constructed graphs at the voxel level in which the nodes represented the brain voxels and the edges represented the inter-voxel FC. The time series of each voxel was extracted from the preprocessed rs-fMRI data to calculate the temporal Pearson's correlation of the time series between all pairs of brain voxels. The computation was restricted to a gray-matter mask (N_{voxels} = 45381) in SPM8. Given a gray-matter voxel i, the FCS was computed using the following equation [6,10,22,40]:

$$FCS(i) = \frac{1}{N-1}\sum_{j\neq i} Z_{ij} \quad r_{ij}>0.2$$

where r_{ij} was the Pearson's correlation of the time series between voxel i and voxel j, r_{ij} was converted to z_{ij} using a Fisher Z-transformation to improve normality, and 0.2 is the threshold set to eliminate potentially spurious correlations. Furthermore, the connectivity map was standardized by converting to Z scores to allow the maps to be averaged and compared across participants. Finally, all individual FCS maps were spatially smoothed using a Gaussian kernel (full width at half-maximum = 6 mm). For more details regarding the FCS analysis, see Supplemental Materials.

2.4. Statistical analysis

The statistical analyses of the FCS maps across groups were performed using a voxel-based, one-way analysis of covariance (ANCOVA) with age, gender, and education level as covariates, followed by post hoc two-sample t-tests. A correction for multiple comparisons was performed by Monte Carlo simulations using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf). A corrected significance level of 0.05 was obtained with a combined $P < 0.01$ and cluster size $> 1{,}728\ mm^3$ for the ANCOVA analysis and a combined $P < 0.01$ and cluster size $> 918\ mm^3$ for the post hoc two-sample t-test analysis (which was conducted within a mask showing the group FCS differences from the ANCOVA analysis). To identify the brain-behavior relationship, we first examined the relationships between the FCS and clinical variables (i.e., hearing loss duration and hearing level) in the 38 SD patients across the whole brain. Then, the relationship between the FCS and clinical variables was separately analyzed in the LD and RD groups.

Recently, voxel-level thresholds below 0.001 have been recommended to control the false positive rates in cluster-level inference [12]. In our study, because the subjects were relatively heterogeneous and the sample size in each cohort was small, the detection power was considerably reduced. Indeed, no clusters survived at the voxel-wise thresholds of 0.001. Thus, we used the voxel-level correction threshold of 0.01 to balance the control over false positives and the maintenance of sufficient power to detect differences.

3. Results

3.1. Sample characteristics

Table 1 summarizes the participants' clinical and demographic characteristics. No group differences ($P > 0.05$) in age, gender or educational level were observed. In the two patient groups, both the duration of hearing loss and the hearing levels were not significantly different ($P > 0.05$).

3.2. FCS differences among the LD patients, RD patients and HCs

The FCS maps of the three groups are presented in Fig. 1. In the HC group, the brain regions with a higher FCS were mainly distributed in several default mode network (DMN) regions (mainly involving the

Table 1
Summary of the demographic and clinical data.

Group	LD	RD	HC	P value
Male/Female	5/12	7/14	9/12	0.666[a]
Age (years)	46.6 ± 11.9	50.1 ± 9.5	43.8 ± 7.0	0.106[b]
Education (years)	9.88 ± 2.8	11.43 ± 3.3	11.2 ± 4.3	0.376[b]
PTA of left ear (dB)	65.7 ± 18.5	15.1 ± 3.0	13.0 ± 1.7	< 0.001[b]
PTA of right ear (dB)	15.0 ± 3.0	76.6 ± 30.8	13.1 ± 1.4	< 0.001[b]
Disease duration (months)	37.9 ± 14.1	44.0 ± 13.6	NA	0.701[c]

Note: LD, left-sided deafness; RD, right-sided deafness; HC, healthy control; PTA, pure tone average.
[a] p-value was obtained using a Pearson Chi-square test (two-tailed).
[b] p-value was obtained using one-way ANOVA (two-tailed).
[c] p-value was obtained using the independent-sample t-test (two-tailed).