Original Article

Investigation of functional connectivity in Bell's palsy using functional magnetic resonance imaging: prospective cross-sectional study

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Background: The most common cause of lower motor neuron facial palsy is Bell's palsy (BP). BP results in partial or complete inability to automatically move the facial muscles on the affected side and, in some cases, to close the eyelids, which can cause permanent eye damage. This study investigated changes in brain function and connectivity abnormalities in patients with BP.

Methods: This study included 46 patients with unilateral BP and 34 healthy controls (HCs). Resting-state brain functional magnetic resonance imaging (fMRI) images were acquired, and Toronto Facial Grading System (TFGS) scores were obtained for all participants. The fractional amplitude of low-frequency fluctuation (fALFF) was estimated, and the relationship between the TFGS and fALFF was determined using correlation analysis for brain regions with changes in fALFF in those with BP versus HCs. Brain regions associated with TFGS were used as seeds for further functional connectivity (FC) analysis; relationships between FC values of abnormal areas and TFGS scores were also analyzed.

Results: Activation of the right precuneus, right angular gyrus, left supramarginal gyrus, and left middle occipital gyrus was significantly decreased in the BP group. fALFF was significantly higher in the right thalamus, vermis, and cerebellum of the BP group compared with that in the HC group ($P<0.05$). The FC between the left middle occipital gyrus and right angular gyrus, left precuneus, and right middle frontal gyrus increased sharply, but decreased in the left angular gyrus, left posterior cingulate gyrus, left middle frontal gyrus, inferior cerebellum, and left middle temporal gyrus. Furthermore, the fALFF in the left middle occipital gyrus was negatively correlated with TFGS score ($R=0.144$; $P=0.008$).

Conclusions: The pathogenesis of BP is closely related to functional reorganization of the cerebral cortex. Patients with BP have altered fALFF activity in cortical regions associated with facial motion feedback monitoring.

Keywords: Bell's palsy (BP); fractional amplitude of low-frequency fluctuation (fALFF); functional connectivity; functional magnetic resonance imaging (fMRI)

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Introduction

The most common cause of lower motor neuron facial palsy is Bell's palsy (BP). BP results in a partial or complete inability to automatically move the facial muscles on the affected side (1). BP may be distressing to patients and even lead to a psychological inferiority complex, thereby creating social barriers and decreasing quality of life. Noninvasive diagnostic testing may play an important role in predicting the long-term prognosis of BP and guiding and monitoring treatment, especially at an early stage of the disease (2).

Functional magnetic resonance imaging (fMRI) is an MRI technique that reflects the brain's functional state. Fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) are commonly used to measure the fMRI signals of local spontaneous neural activity (3). fMRI has been widely used in previous studies on BP. For example, Klingner *et al.* found that people with BP had reduced brain connectivity, mainly in areas responsible for sensorimotor integration and supervision (4). In addition, patients with unilateral BP were found to have hyperactivity in the brain region contralateral to the affected side, which may be associated with motor integration and subsequent motor integration and control (4). Another finding in patients with BP is that the cerebellum and cerebral cortex act on pathological sensorimotor processing, unlike in healthy controls (HCs) (5,6). Furthermore, in patients with BP, brain regions associated with the primary sensory and motor cortex had significantly abnormal ReHo or fALFF values compared with values in HCs (7). These studies also indicate that resting-state fMRI may be a sensitive tool for observing early plasticity in patients with BP. Han *et al.* calculated fALFF values in patients with BP (within 14 days of onset) using resting-state fMRI and divided patients into those with left-sided paralysis and those with right-sided paralysis, and found that the regulatory mechanisms differed between patients with left and right early BP (8).

The severity of BP is also associated with changes in the function of certain brain regions (8). One study that analyzed voxel-based morphometry (VBM) and resting-state fMRI noted that the recovery of BP was complemented by cortical reorganization, with significant changes in functional connectivity (FC) prior to clinical recovery (9). Other studies have shown that patients with BP with dysarthria have several FC changes in brain language networks. The severity of oral paralysis was associated with these functional changes (10).

According to the clinical symptoms and existing studies on BP, it can be speculated that the improvement and pathogenesis of BP are closely related to the functional reorganization of the cerebral cortex. We therefore hypothesized that patients with BP would have intrinsic functional activities for abnormalities in several brain regions: (I) altered fALFF activity in cortical areas associated with monitoring of motor feedback and facial movements, and (II) fALFF-based alterations in brain areas with abnormal FC. To validate this hypothesis, fALFF was calculated and compared between the BP and HC groups, and correlations between fALFF values in different brain regions and clinical performance scores were analyzed. In addition, brain regions associated with clinical performance scores and fALFF values were identified as regions of interest (ROI). Finally, we analyzed the changes in resting-state brain FC in patients with BP. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-911/rc).

Methods

Participants

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the China-Japan Friendship Hospital (Beijing, China) approved this prospective cross-sectional study. All participants were informed about the study and provided written informed consent.

Between November 2017 and March 2019, consecutive patients with BP attending the China-Japan Friendship Hospital were recruited to the study. The Toronto Facial Grading System (TFGS) (11) score was measured for each participant. A clinical diagnosis of facial nerve palsy and the TFGS score were confirmed by 2 senior neurologists with 10-year experience. To be included in the study, patients had

to meet the following criteria: (I) first-ever idiopathic one-sided facial nerve palsy confirmed by 2 physicians, and (II) right-handedness. Age- and sex- matched healthy volunteers were recruited from the local community according to the following inclusion criteria: (I) a TFGS score of 100 points and (II) right-handedness. All participants were age >18 and <65 years. The exclusion criteria for all participants were the following: (I) other neurologic and psychiatric diseases, (II) metabolic disease, (III) alcohol or drug abuse, (IV) MRI contraindications, and (V) abnormal findings on brain imaging.

MRI acquisition

A 3.0-T MRI system was used (Discovery MR750; GE Healthcare, Chicago, IL, USA) with a supporting head quadrature coil. Each participant was required to rest in a supine position with their eyes shut, breathe regularly, and reduce head motions. They were also asked to continue to stay awake and not to think, and to wear rubber earplugs to reduce noise. The parameters for the axial resting-state fMRI with a single-shot gradient recalled echo-planar imaging sequence were as follows: field of view (FOV), 240×240 mm^2; slice thickness, 3.5 mm; slice gap, 0.7 mm; repetition time (TR)/echo time (TE)/flip angle, 2,000 ms/30 ms/90°; matrix, 64×64; and number of excitations (NEX), 1.34 slices with 240 phases collected. The parameters of sagittal 3-dimensional fast spoiled gradient-echo sequences (3D-FSPGR) for 3D-T1 anatomic data were as follows: FOV, 256×256 mm^2; acquisition matrix, 256×256; TR, 6.7 ms; TE, min full; slice thickness, 1.0 mm; and NEX, 1.

Data preprocessing

All fMRI images in Digital Imaging and Communications in Medicine (DICOM) format were first converted into Neuroimaging Informatics Technology Initiative (NIFTI) format, and the first 10 time points discarded. Data preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF) Advanced Edition package (12). Specifically, slice-timing rectification and motion correction (standard 2.0° or 2 mm) were performed and followed by the separation of the head motion parameters from the data for all participants. Spatial normalization was completed by using T1 anatomical images with unified segmentation. Spatial smoothing was directed with the full width at half maximum (FWHM) set up at 4 mm, and linear drift was taken off. Covariate regression was then performed: the cerebrospinal fluid (CSF) region and white matter signals were extracted, linear fitting was directed on the time series signals in the CSF regions and white matter, and the CSF and the white matter signals were subtracted from the whole signal. Then, band pass filtering (as 0.01–0.10 Hz) was performed to remove the effects of low-frequency drift and high-frequency noise, and frequencies were set. To make images for patients with left-sided palsy and their age- and sex-matched HCs comparable to images of patients with right-sided palsy and their age- and sex-matched HCs, the NIFTI files of patients with left-sided palsy were flipped so the BP was on the right before analysis and data processing (4).

Whole-brain fALFF analysis

After the time series of the whole-brain blood-oxygen-level-dependent (BOLD) signal had been obtained, the fALFF value, as an index, was used to analyze the resting state fMRI data. The time series of each voxel in brain BOLD images was transformed to the frequency domain, and the power spectrum's square root was computed as the fALFF. The fALFF value was further divided by the global mean fALFF value to standardize the data within each group. The normalized fALFF value was then divided by the entire band's fALFF value to obtain each voxel's normalized fALFF value. Then, z-standardization was performed on the fALFF map in terms of voxels. A whole-brain fALFF voxel-wise analysis was conducted between the BP and HC groups.

ROI-based correlation analysis

The fALFF value was normalized by z-transformation using MATLAB-based software REST (http://www.restfmri.net/forum/REST). ROIs delineated brain regions with significantly increased or decreased activation on the image. Subsequently, the z-transformed fALFF was extracted from the ROI in the BP group, and an ROI-based correlation analysis was performed between the z-transformed fALFF value and TFGS score.

Voxel-wise FC analysis

After correlation analysis, brain areas in which the fALFF had a significantly high correlation with TFGS score were selected as the "seeds" for seed-to-voxel FC analysis. Specifically, the "seed" is a spherical ROI with a radius of 3 mm centered on the peak coordinates of the significantly correlated brain region.

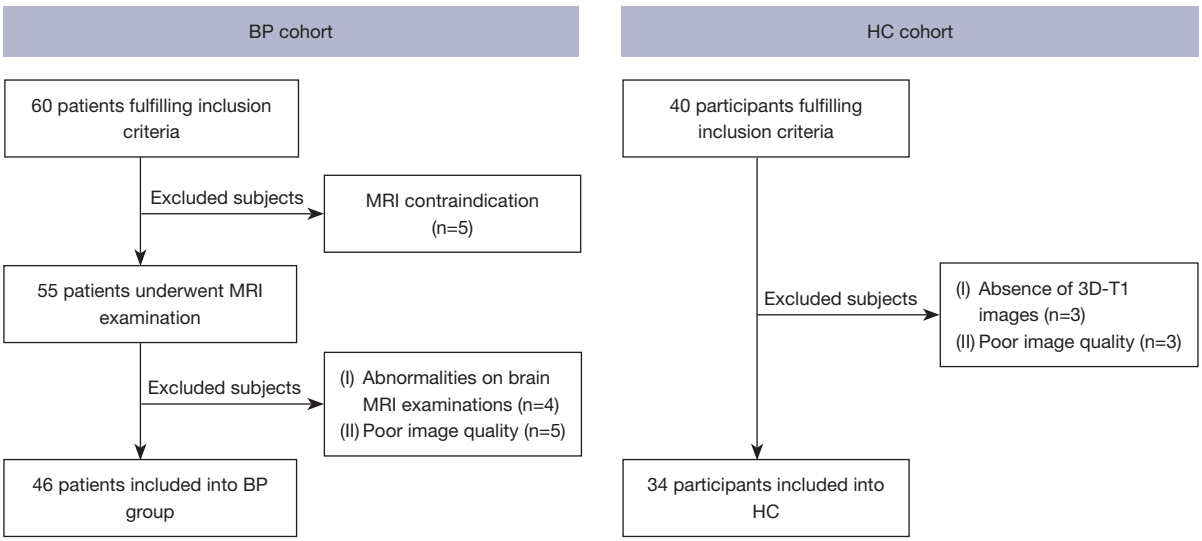

Figure 1 Flowchart showing the selection of participants for this study. BP, Bell's palsy; 3D, three-dimensional; HC, healthy control; MRI, magnetic resonance imaging.

Table 1 Demographic and clinical data of the study population

Group	BP	HC	P value
Sex (males/females)	15/31	14/20	0.485
Age (years)	43.33±13.88	46.18±14.38	0.665
Education (years)	12.80±4.41	14.13±2.33	0.234
TFGS score	20.41±18.67	100±0.00	<0.001

Unless indicated otherwise, data are given as the mean ± SD. The significance of differences between the BP and HC groups in age and education were calculated using independent 2-sample *t*-tests. The significance of differences in sex were calculated using chi-squared tests. The lower the TFGS score is, the more severe the symptoms of facial paralysis. BP, Bell's palsy; HC, healthy control; SD, standard deviation; TFGS, Toronto Facial Grading System.

Statistical analysis

The demographic and clinical data of the study population were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of data distribution. Sequential data are presented as the mean ± standard deviation (SD). Differences in age and years of education between the BP and HC groups were compared using 2-sample *t*-tests. Differences in sex between groups were tested using the χ^2 test, and the threshold for significance was P<0.05.

The voxel-wise group comparisons between the BP and HC groups for fALFF and FC values were made using 2-sample *t*-tests, which were conducted using DPARSF. Age, sex, and education were induced as covariates in all statistical models. The family-wise error (FWE) correction method was used for multiple comparisons with a threshold of 0.05. Correlations between z-transformed fALFF values and TFGS score were assessed using Pearson correlation coefficient, with significance set at an FWE-corrected P value <0.05.

Results

Demographic and clinical characteristics

A flowchart of the selection process for participants is shown in *Figure 1*. In all, 46 patients with unilateral BP (15 male; mean age 43.33±13.88 years; 22 left-sided BP; 24 right-sided BP) and 34 healthy volunteers (14 male; mean age 46.18±14.38 years) as the control group were included in the study. There were no significant differences in age, sex, or education between the 2 groups (all P values >0.05). The TFGS score of the BP group (20.41±18.67) was lower than that of the HC group (100.00±0.00). The demographic and clinical characteristics of all participants are summarized in *Table 1*.

Differences in fALFF between the BP and HC groups

Compared with that in the HC group, there was significantly

Table 2 Differences in fractional low-frequency fluctuation amplitude between the BP and HC groups

Brain region	Cluster size	Peak MNI coordinates (mm; x, y, z)	Peak *t* value	Z scores of fALFF	
				BP	HC
BP < HC					
PCUN.R	779	3, –69, 33	13.86	0.14±0.16	1.37±0.21
ANG.R	295	48, –64, 27	9.68	0.08±0.18	1.27±0.34
SMG.L	32	–63, –36, 27	8.12	0.09±0.29	1.17±0.42
MOG.L	76	–42, –72, 36	7.78	0.03±0.26	1.28±0.39
BP > HC					
Vermis	44	0, –48, –39	8.71	0.05±0.31	–1.02±0.46
THA.R	36	12, –18, 12	8.15	0.13±0.20	–0.82±0.42
Inferior cerebellum	21	9, –63, –33	7.61	0.17±0.16	–0.59±0.20

The statistical threshold was set at a family wise error-corrected P value <0.05. Unless indicated otherwise, data are presented as the mean ± SD. ANG.R, right angular gyrus; BP, Bell's palsy; fALFF, fractional amplitude of low-frequency fluctuation; HC, healthy control; MNI, Montreal Neurologic Institute; MOG.L, middle occipital gyrus left; PCUN.R, right precuneus; SD, standard deviation; SMG.L, left supramarginal gyrus; THA.R, right thalamus.

decreased activation at the right precuneus, right angular gyrus (ANG.R), left supramarginal gyrus, and left middle occipital gyrus (MOG.L) in the BP group (*Table 2*; *Figure 2*). In the BP group, the right thalamus, vermis, and right inferior cerebellum had significantly higher fALFF values than in the HC group.

Correlation results

Figure 3 shows the differences in fALFF values between the HC and BP groups. Correlation analysis showed that only the fALFF of the MOG.L was negatively correlated with the TFGS score (R=0.144; P=0.008) after FWE correction. In contrast, there was negligible correlation between FC and TFGS scores for the remaining brain areas.

Differences in FC between the BP and HC groups

In contrast to the HC group, the correlation area between fALFF and TFGS score in the BP group was taken as the ROI. Then the FC for the HC and BP groups was calculated separately. Compared with the HC group, the BP group had significantly increased FC between the MOG.L and ANG.R and between the left precuneus and right middle frontal gyrus (MFG), but markedly decreased FC between the left angular gyrus, left posterior cingulate gyrus, left MFG, inferior cerebellum, and left middle temporal gyrus (*Table 3*; *Figure 4*).

Discussion

In this study, we combined fALFF and FC analysis methods based on mechanisms of brain coactivation between different regions. Specifically, we sought to detect FC patterns in regions where fALFF activation was abnormal and correlated with paralysis severity. To the best of our knowledge, this is the first study to examine patients with BP via FC analysis based on ROIs that are brain regions related to paralysis severity.

We found reduced activation in the precuneus in patients with BP compared with the HC group. The precuneus is interlinked with various brain structures, making it a component of many systems. Thus, the precuneus is involved in many functions that generate complex human behavior, including episodic memory, visuospatial abilities, motor control, self-perception, awareness, and executive and working memory (13). Greater activity is exhibited by the precuneus during rest than when responding to external tasks (14). The precuneus has strong connections to both the supraoccipital and parietal cortices, which are known to be involved in motor image information processing (15-17). Motor imagery is defined as a mental simulation of motor behavior (18-20) and includes implicit or explicit motor preparation, passive observation of movements, and mental manipulation of sensorimotor representations. We speculate that unilateral paralytic symptoms in patients with BP may contribute to changes in the difference between the

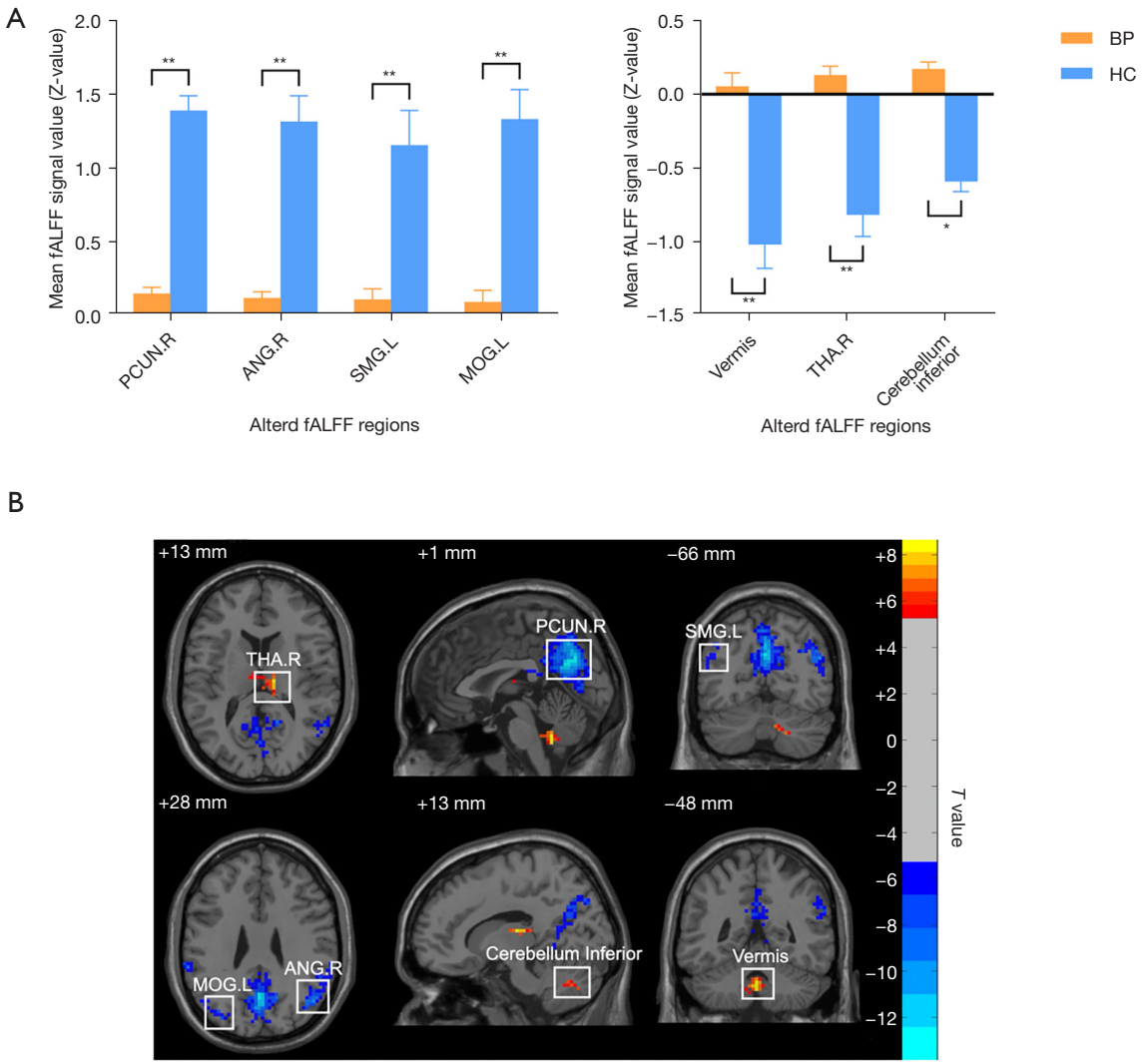

Figure 2 Differences in fALFF between the BP and HC groups. (A) Comparison of fALFF (mean ± SD) between the HC and BP groups. There were significant differences in fALFF of brain regions between the 2 groups (family-wise error-corrected P value <0.05). *, P<0.05; **, P<0.01. (B) Compared with those in the HC group, fALFF values in the PCUN.R, ANG.R, SMG.L, and MOG.L were lower, whereas those in the THA.R, vermis, and right inferior cerebellum were higher in the BP group. Blue areas represent regions with decreased spontaneous neuronal activity, whereas red areas represent regions with increased spontaneous neuronal activity. ANG.R, right angular gyrus; BP, Bell's palsy; fALFF, fractional amplitude of low-frequency fluctuation; HC, healthy control; MOG.L, left middle occipital gyrus; PCUN.R, right precuneus; SD, standard deviation; SMG.L, left supramarginal gyrus; THA.R, right thalamus.

preparation of facial movements and the outcome of sensory reception, leading to precuneus abnormalities. Uddin *et al.* showed that the precuneus is part of the default mode network (DMN), and its functional activity in the DMN is highly activated during the resting state and during periods of cognitive activity (21). Our study may indicate a clear difference in the DMN in patients with BP compared with HCs.

Compared with that in the HC group, the fALFF region was abnormal in patients with BP and the only brain region negatively correlated with the TFGS score was the MOG.L. The occipital lobe contains most of the visual cortex's anatomical area, facilitates communication and visual information processing with the cerebral cortex, and plays a role in the perception of facial emotions. The role of the MOG in the modulation of involuntary face processing by

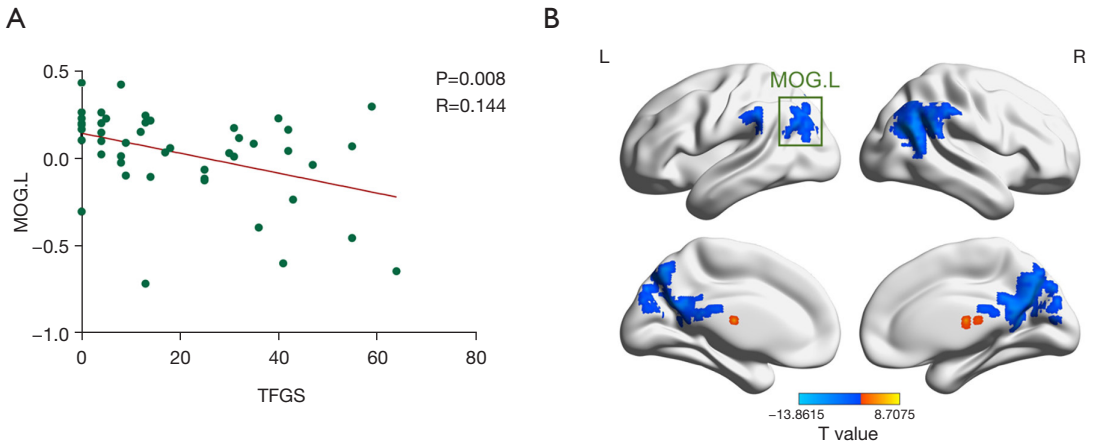

Figure 3 Correlation between fALFF and TFGS scores in patients with BP. (A) There was a positive correlation between fALFF values of the MOG.L and TFGS scores. (B) The green square indicates the cluster located in the MOG.L with different fALFF values between the BP and HC groups. BP, Bell's palsy; fALFF, fractional amplitude of low-frequency fluctuation; L, left; R, right; MOG.L, left middle occipital gyrus; TFGS, Toronto Facial Grading System.

Table 3 Differences in functional connectivity between the Bell's palsy and healthy control groups

Brain region	Cluster size	Peak MNI coordinates (mm; x, y, z)	Peak *t* value	Z scores of FC	
				BP	HC
BP < HC					
ANG.L	465	–57, –60, 27	13.13	0.21±0.13	0.34±0.12
PCG.L	820	–3, –45, 24	11.74	0.24±0.15	0.31±0.13
MFG.L	959	–33, 27, 42	9.53	0.15±0.10	0.24±0.07
Cerebellum	157	42, –72, –48	9.00	0.15±0.11	0.22±0.11
MTG.L	76	–63, –33, –15	8.34	0.15 0.12	0.23±0.11
BP > HC					
ANG.R	305	42, –66, 36	10.23	0.27±0.12	0.33±0.13
PCUN.L	787	–3, –57, 27	10.00	0.25±0.15	0.30±0.13
MFG.R	327	27, 30, 45	9.76	0.22±0.11	0.25±0.08

The statistical threshold was set at a family wise error-corrected P value <0.05. Unless indicated otherwise, data are presented as the mean ± SD. ANG.L: left angular gyrus; ANG.R, right Angular; BP, Bell's palsy; Cerebellum, inferior cerebellum; HC, healthy control; MFG.L, left middle frontal gyrus; MFG.R, right middle frontal gyrus; MNI, Montreal Neurologic Institute; MTG.L, left middle temporal gyrus; PCG.L, left posterior cingulate gyrus; PCUN.L, left precuneus; SD, standard deviation.

category-selective attention has been demonstrated, and it has been found that during involuntary face processing, the activation of MOG under face-selective attention is reduced (22). The decrease in fALFF may be driven by symptoms of BP because patients with BP have impaired visual input due to paralysis.

The FC study showed that the left MOG may act as a connection in the resting state to participate in the processing and compensatory behavior of patients with BP due to monitoring of motor feedback and facial movements. These findings may enhance our understanding of neurobiological mechanisms in patients with BP.

In addition, the ANG.R also showed a unique decrease in activation. Monitoring self-action feedback in meaningful

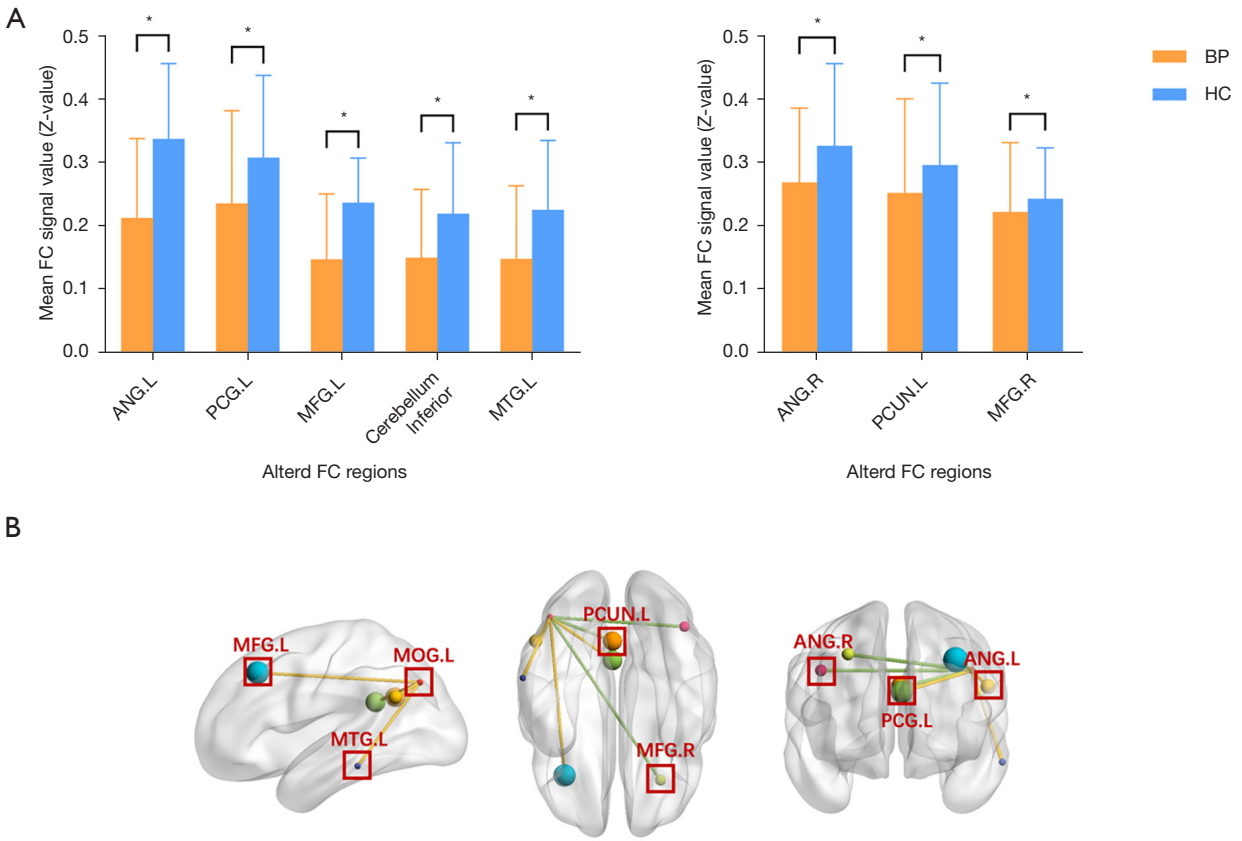

Figure 4 Differences in FC between the BP and HC groups. (A) Comparison of FC (mean ± SD) between the HC and BP groups. There were significant differences in FC in different brain regions between the 2 groups (family wise error-corrected P value <0.05). *, P<0.05. (B) Patterns of increased FC in the BP group. The FC between the MOG.L and the ANG.R and between the PCUN.L and MFG.R was significantly increased (green), whereas FC values were significantly decreased (yellow) in the ANG.L, PCG.L, MFG.L, inferior cerebellum, and MTG.L in the BP group compared with the HC group. ANG.L, left angular gyrus; ANG.R, right angular gyrus; BP, Bell's palsy; FC, functional connectivity; HC, healthy control; MFG.L, left middle frontal gyrus; MFG.R, right middle frontal gyrus; MOG.L, left middle occipital gyrus; MTG.L, left middle temporal gyrus; PCG.L, left posterior cingulate gyrus; PCUN.L, left precuneus.

interactions with the outside world is extremely important. This process compares sensory predictions with actual motor feedback and contributes to motor learning and to distinguishing between self-generated and externally generated stimuli. Abnormalities are detected in the ANG when agency (i.e., "my sense of causing a behavior") is violated (23-26). The ANG may be involved in more normal sensory conflict detection (27). van Kemenade *et al.* found that the ANG is not only associated with perceptual areas, but may also act as a mediator between perception and interpretation during action outcome processing (28). In our study, the ANG.R was abnormal in patients with BP. This may be related to the discrepancy between perceived and actual facial movements in patients with facial paralysis when performing movements related to the facial muscles, or it could be related to involuntary abnormal facial expressions and movements.

We also found a decrease in the FC of the ipsilateral MOG with the ANG and MFG. Japee *et al.* found that the MFG is primarily responsible for coordinating disparate messages (29). The ANG acts as a cross-modal center and plays an important role in combining and integrating multisensory information (30). The MFG is involved in the processing and recognition of temporal differences in motor feedback monitoring (27). There is also intrinsic connectivity between the sensorimotor areas of the cerebellum and visual areas located in the middle temporal gyrus (31). Due to the characteristic of contralateral

control of the brain, patients with right-sided BP showed a decrease in FC in the left ANG and MFG, along with abnormalities in motor integration. Moreover, the FC of the contralateral ANG and MFG increased, possibly due to the compensatory condition that occurs on the contralateral face in patients with unilateral BP.

Our experimental results also suggest that the cerebellum is one of the brain regions with increased abnormal activation in patients with BP. There is substantial evidence to support the cerebellum as the place in the human brain where sensory predictions are coupled with actual motor feedback. Some fMRI-based studies found that cerebellar activity is significantly lower in trials without than with sensory error (32,33) and that activity in the cerebellum correlates with movement, with the magnitude of the temporal bias between feedbacks being correlated (34).

Moreover, research in patients has repeatedly demonstrated that updating predictions of sensorimotor consequences is impaired in patients with cerebellar damage (35-37). van Kemenade *et al.* reported that the cerebellum is prominently involved in comparative processing during voluntary actions, as its activity is regulated by the nature of the action (self-generated *vs.* externally generated) (27). In addition, studies have shown the cerebellum to be involved in language function (38,39), with the activity of language function being decreased in those with BP; it has been speculated that the cerebellum may increase functional activity as compensation. In a BP-related study, he cerebellum and cerebral cortex were found to work together in long-term adaptation to short-lived pathological sensorimotor processing (6). Klingner *et al.* found that patients with BP had abnormalities in connectivity primarily in areas responsible for sensorimotor integration and supervision, such as the thalamus and cerebellum (4). This is consistent with our finding of abnormal activation of the cerebellum in patients with BP. Taking these findings into consideration with those of previous studies, we speculate that this may be related to the discrepancy between perception and actual facial movements caused by facial paralysis in patients with BP. It may also be related to the oral paralysis symptoms in patients with BP, which also confirms the previous conclusion regarding dysarthria in patients with BP (40).

This study has some limitations. First, each BP patient might have experienced a different treatment regimen or no treatment before data collection, and the effects of treatment and drugs were difficult to eliminate. Second, there was no comparative study between patients with left- and right-sided facial paralysis and the HCs in the present study because the sample size was too small for subgroup analysis. With an increased sample size, it may be possible to undertake such comparative studies in the future. Third, data for all participants was collected once, and it was not possible to effectively conduct longitudinal surveys to track the overall changes before and after treatment. Fourth, most patients had a high degree of paralysis, and the lack of people with a low degree of paralysis might have led to bias in correlation analysis. Finally, this study only used fMRI images, and it was impossible to verify the accuracy of the results from a multimodal perspective.

Conclusions

This cross-sectional analysis highlights that the pathogenesis of BP is closely related to the functional reorganization of the cerebral cortex. Patients with BP have altered fALFF activity in cortical regions associated with facial motion feedback monitoring. This may explain the clinical manifestations of inconsistent and involuntary facial movements in those with BP.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-911/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-911/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of the China-Japan Friendship Hospital approved this prospective cross-sectional study. All participants were informed about the study and provided written informed consent.

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