Original Article

Differences in functional brain alterations driven by right or left facial nerve efferent dysfunction: Evidence from early Bell's palsy

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Background: Bell's palsy is defined as idiopathic unilateral facial nerve palsy. Early Bell's palsy is characterized by emerging asymmetric motor conduction of the facial nerve and obvious imbalance of facial muscle movement, which can result in a substantial psychological impact on patients and trigger brain cortical functional reorganization. However, the differences between the brain functional alterations were driven by right or left facial nerve efferent dysfunction in patients with early Bell's palsy are not fully understood. The neuroimage study in patients with different-sided Bell's palsy in the early stage will help to understand the different mechanisms involved in functional integration driven by unilateral facial efferent nerve dysfunction and to provide the theoretical foundation for the choice of suitable treatment strategy.

Methods: Sixty-seven patients and 37 age- and sex-matched healthy controls were recruited to undergo resting-state functional magnetic resonance imaging (R-fMRI). Regional brain activity was analyzed by comparing the fractional amplitude of low-frequency fluctuations (fALFF) between right palsy and healthy control, left palsy and healthy control, and right and left palsy groups. The altered brain regions were further selected as seeds in subsequent functional connectivity (FC) analysis, and the correlations between the Toronto Facial Grading System (TFGS) scores and the connectivity alterations were also analyzed.

Results: The right and left Bell's palsy groups showed fALFF alterations compared with the healthy control group, and several brain regions with different fALFF values between the right and left palsy groups were identified. In the right palsy group, overall inter-regional FC increased in the right supramarginal gyrus (SMG), bilateral superior frontal gyrus (SFG), and left precentral gyrus (PreCG), compared with the left palsy group. Furthermore, the brain region pairs with higher FC in the right palsy group were left temporal pole of the superior temporal gyrus (TPOsup) and right SMG, left TPOsup and middle cingulate cortex (MCC), left TPOsup and left PreCG, right SMG and SFG, MCC and left PreCG, left and right SFG, and right SFG and left PreCG. In the right palsy group, the left TPOsup and PreCG showed a negative correlation with the TFGS score, while the right SFG and left PreCG showed a positive correlation with the TFGS scores. In the left palsy group, the left TPOsup and right SMG, and the right SMG and SFG region pairs showed a negative correlation with the TFGS score.

Conclusions: The fALFF and FC analyses revealed the remodeling of different brain functional networks driven by right or left facial nerve efferent dysfunction in patients with early Bell's palsy. The reintegration mechanisms differed between patients with right and left Bell's palsy. Additionally, the severity of the disease

showed different associations with altered FC.

Keywords: Resting-state functional magnetic resonance imaging (R-fMRI); Bell's palsy; fractional amplitude of low-frequency fluctuation (fALFF); functional connectivity (FC); brain network

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Introduction

Peripheral facial palsy is a condition in which facial nerve efferent dysfunction results in an inability to control the facial muscles on the affected side. Approximately 80% of the cases of facial nerve paralysis is idiopathic and unilateral and thus define as Bell's palsy (1,2). The facial nerve is the main motor pathway to the facial muscles and is involved in regulating facial expression, movement, and other functions (3,4). Bell's palsy is characterized by asymmetric motor conduction of facial nerve branches and imbalance of facial muscles movement, which may result in a substantial psychological impact on the patient and trigger brain cortical reorganization (5). Thus, research on brain function alterations related to this condition will facilitate the understanding of the mechanisms of functional integration within the cerebral cortex (6).

Functional magnetic resonance imaging (fMRI) is an advanced technique, widely applied in the evaluation of numerous diseases, including peripheral facial palsy (7,8). An interesting fMRI approach involves imaging the brain neural network by examining functional connectivity (FC) when the individual does not focus on external stimuli, and the brain is at wakeful rest (9-11). Conducting fMRI of brain activity in the resting state requires less patient cooperation compared with the same analysis during complex activation tasks. Previous studies on Bell's palsy have often focused on task-fMRI, which indicated that some cortical functional connectivities are interrupted in the early phase, with an increase in motor integration. Functional integration mainly occurs in the hemisphere contralateral to the paralyzed side (12-14). The FC between the significant motor cortex and other related brain regions gradually recovered to the average level when facial nerve function was gradually recovered (15-17).

The resting-state fMRI (R-fMRI) offers a wealth amount of helpful information for detecting functional brain changes and interpret the results of task-fMRI, as the brain is somewhat active even when no task is being performed (18,19). Both the amplitude of low-frequency fluctuation (ALFF) and the fractional amplitude of low-frequency fluctuation (fALFF) can reflect the spontaneous activity of the brain from the perspective of brain energy metabolism in R-fMRI (20). fALFF is more sensitive and specific than ALFF at low frequencies and can more accurately reflect the strength of spontaneous activity in the brain (21). FC is another commonly used quantification method, defined as the temporal series correlation among corresponding functionally activated events (22). However, research using R-fMRI in patients with peripheral facial palsy is still in its initial stages (23). Recent studies have revealed that in patients with facial paralysis, the FC between the ipsilateral anterior cingulate gyrus and other related brain areas is enhanced, and such enhancement is related to cortical reconstruction during rehabilitation (24). Changes in the default mode network (DMN) have been linked to the altered brain state in the patients with Bell's palsy. The DMN is the distinct brain network connecting the regions that are most active when the brain is at rest, such as the medial temporal lobe, medial prefrontal cortex, and posterior cingulate cortex, known to be highly correlated with each other (25). In patients with facial nerve paralysis, the functional connectivities of the regions in the DMN show changes depending on the pathological states, which may involve various interacting brain regions related to sensory, motor, emotion, and cognitive functions (25). However, for patients with right or left early stage Bell's palsy, studies on the bilateral differences in abnormal functional activities using fALFF and FC are rare. The association of altered FC with clinical presentations is not yet clear. Investigation of patients with different-sided Bell's palsy in the early stage would be helpful to gain insight into the different mechanisms involved in functional integration driven by unilateral facial efferent nerve dysfunction and to provide a neuroimage foundation for a suitable treatment strategy to be implemented as early as possible in the course of the disease.

In the current study, we hypothesized that several abnormal brain intrinsic functional activities in various brain regions would be found in patients with early-stage right or left Bell's palsy. Furthermore, since score criteria regarding the clinical presentation were shown to be important in rating facial nerve injury and disability, we also hypothesized that they would partially reveal the differences between patients and healthy controls. We tested this hypothesis using R-fMRI to examine the fALFF, and the brain areas with abnormal fALFF were selected as seeds in the following FC analysis. Besides, correlations between altered FC and clinical presentation scores were analyzed in the left and right palsy groups.

Methods

Subjects

The Ethics Committee of our hospital approved this study and written informed consent was obtained from all patients before the study began. Sixty-seven patients were enrolled. The inclusion criteria were: (I) first-ever idiopathic unilateral facial nerve palsy (two physicians confirmed the diagnosis); (II) right-handed; and (III) onset time of 2–7 days. Patients with a history of neurologic, metabolic, or psychiatric disorders, or who were using psychotropic drugs, were excluded. The patients were divided into a right facial paralysis group (34 cases, 13 men and 21 women, mean age 47.27±12.96 years) and left facial paralysis group (33 cases, 12 men and 21 women, mean age 48.11±13.27 years). Thirty-seven healthy controls (14 men and 23 women, mean age 46.05±13.65 years) were recruited from graduate students, the local community, and the hospital staff. The inclusion criteria were: (I) no history of neurologic, metabolic, or psychiatric diseases, and not currently using psychotropic drugs; (II) no family history of neurological diseases; (III) normal conventional head MRI examination results; (IV) Toronto Facial Grading System (TFGS) (26) scores of 100 points; and (V) being right-handed. The TFGS score was evaluated for each participant.

MRI data acquisition

Participants were required to rest in a supine position with their eyes closed, breath regularly, and to minimize head movements. Also, they were asked to remain awake and not to think, and to wear rubber earplugs to reduce noise. We used a 3.0 T MR imaging system (GE healthcare, Discovery MR750, Milwaukee, WI, USA) with a supporting head quadrature coil. The parameters of axial resting state blood oxygen-level dependent-fMRI were: repetition time (TR) =2,000 ms, echo time (TE) =30 ms, slice thickness =3.5 mm, slice spacing =0.7 mm, field of view (FOV) =240 mm × 240 mm, matrix =64×64, flip angle =90°, and number of excitations (NEX) =1, 34 slices and 240 phases; The parameters of sagittal 3D T1 weighted image with three-dimensional fast spoiled gradient-echo sequences (3D FSPGR) were: TR =6.7 ms, TE = min full, slice thickness =1.0 mm, FOV =256 mm × 256 mm, acquisition matrix =256×256, and NEX =1.

Data processing and analysis

Data pre-processing

The Data Processing Assistant for Resting-State fMRI (DPARSF, Advanced Edition) software was used (27). The preprocessing procedure was as follows: First, the data format was converted from DICOM to NIFTI. Next, the first ten time points were removed, slice-timing correction and head motion correction (standard 2.0 mm or 2°) were performed, and the head movement parameters were extracted from all participant data. Spatial normalization was then achieved through T1 anatomical images with unified segmentation. Spatial smoothing was conducted with the Full Width at Half Maximum set at 4, and linear drift was removed. Covariate regression was then carried out [the white matter and cerebrospinal fluid (CSF) region signals were extracted, linear fitting was conducted on the time series signals in the white matter and CSF regions, and the signals of the white matter and CSF were removed from the overall signal]. Finally, fALFF calculation and band-pass filtering (frequencies set as 0.01–0.08 Hz), to remove the effects of high-frequency noise and low-frequency drift, were performed.

fALFF and FC analysis

We employed the fALFF value as an index to analyze the R-fMRI data. The time series of each voxel obtained from preprocessed data was converted to the frequency domain using a fast Fourier transform, and the square root of the power spectrum was computed as the ALFF. The ALFF value was further divided by the global mean ALFF value to standardize the data within each group. Then, the normalized ALFF value was divided by the ALFF value of the entire band to obtain the normalized fALFF value of each voxel. The fALFF values were compared between each pair of groups to select the region of interest (ROI) to be

Table 1 Demographic and clinical data of the study population

Groups	Gender (M/F)	Age (years)	Education (years)	Duration (days)	TFGS (scores)
Right Bell's palsy	13/21	47.27±12.96	12.38±2.85	4.52±2.46	17.23±16.22
Left Bell's palsy	12/21	48.11±13.27	11.76±3.15	4.83±2.14	18.71±16.09
Healthy controls	14/23	46.05±13.65	14.13±2.33	0	100.00
P value	0.478	0.124	0.089	0.367*	0.282*

Values are expressed as mean ± SD. *, P value calculated between right and left Bell's palsy with an independent two-sample *t*-test. TFGS, Toronto Facial Grading System.

used in the following FC computation.

The peak coordinates of the regions with altered fALFF values were used as the centers of 6-mm spherical seed brain ROIs, created with the wfu_pickatlas tool of the SPM12 software (28). We computed the time serial correlation coefficient between every pair of ROIs. Then, we computed the mean overall FC of each brain region with the other brain regions. The areas of the bilateral middle cingulate cortex (MCC), altered in the comparison between right and left palsy groups, were in close contact and were considered a unified larger region in the FC analysis because of their unclear boundaries.

Statistical analyses

The demographic and clinical data of the study population were analyzed with SPSS (version 23.0, IBM Corp., Armonk, NY, USA). The age and education level among the three groups were compared by one-way analysis of variance (ANOVA). The palsy duration and TFGS scores were compared, by two-sample *t*-tests, only between the right and left Bell's palsy groups. The chi-squared test was used to compare the sex ratio among the three groups. A one-way analysis of covariance (ANCOVA) was applied to compare the differences in fALFF among the three groups with age, sex, education level, and head movement parameters as covariates. Post hoc *t*-tests were performed to identify the inter-group differences between right palsy and healthy control groups, left palsy and healthy control groups, and right and left palsy groups. The false discovery rate (FDR) correction was used for multiple comparisons in the fMRI data analysis with a threshold of 0.05 (29).

Fisher z-values were extracted from the correlation coefficients by Fisher's transformation, and used in multiple regression across all patients, with age, sex, and education level set as confounding covariates. A two-sample *t*-test was used to compare the means of the overall FC of each ROI with other regions between the right palsy and healthy control groups, left palsy and healthy control groups, and right and left palsy groups. Also, the difference in the FC of every pair of ROIs was analyzed between each pair of groups. FDR correction was performed with a threshold of 0.05. A two-tailed Pearson correlation analysis was performed between the TFGS scores of the patients in each palsy group and the corresponding functional connectivity between paired ROIs, and P values <0.05 were considered statistically significant.

Results

Clinical data

The results indicated no significant differences in sex, age, and education level among the two patient groups and the control group (P>0.05). The time from onset to examination was set to 0, and the TFGS score was equal to 100 for the healthy controls. The palsy duration (mean ± standard deviation: right palsy, 4.52±2.46 days; left palsy, 4.83±2.14 days) and TFGS scores (mean ± standard deviation: right palsy, 17.23±16.22; left palsy, 18.71±16.09) were compared between the right and left patient groups, and no significant differences were found (P>0.05) (*Table 1*).

Differences among the three groups

A significant statistical difference in fALFF was found among the right palsy, left palsy, and healthy control groups, and the post hoc *t*-tests revealed significant differences between all three group pairs (*Table 2*).

Differences between the right palsy and healthy control groups

Compared with healthy controls, the right Bell's palsy group showed significantly increased fALFF values in the right

Table 2 Brain regions showing fALFF differences between every two groups

Brain regions	BA	Peak MNI coordinates (mm) (x, y, z)	t value
Right *vs.* healthy control			
ITG.R	20	(57, –15, –30)	2.46
ORBinf.R	38	(33, 15, –21)	2.56
ORBmid.L	11	(–18, 54, –15)	3.32
ORBsup.L	11	(–12, 66, –12)	2.72
TPOsup.L	38	(–54, 15, –12)	2.61
Caudate.L	25	(–9, 15, –6)	2.54
ACC.L	11	(–11, 39, –3)	2.78
ACC.R	11	(9, 42, 0)	2.44
IFGtriang.L	45	(–54, 24, 3)	2.58
MCC.L	23	(–18, –30, 39)	3.11
MCC.R	23	(9, –12, 36)	2.57
IPL.L	40	(–30, –48, 45)	2.68
Left *vs.* healthy control			
Rectus.L	11	(–9, 39, –18)	2.92
Rectus.R	11	(6, 42, –15)	2.72
ORBsup.L	11	(–12, 48, –21)	2.83
ORBmid.R	11	(24, 48, –15)	2.73
SFG.R	6	(24, 0, 63)	2.87
PreCG.R	6	(24, –6, 48)	3.03
Putamen.R	–	(24, –6, 12)	2.82
Right *vs.* left			
TPOsup.L	38	(–51, 10, –6)	2.19
SMG.R	48	(66, –37, 27)	2.21
MCC.L	23	(–5, –19, 36)	2.48
MCC.R	23	(5, –18, 35)	2.36
SFG.L	6	(–16, 14, 53)	2.79
SFG.R	8	(25, 14, 64)	–2.65
PreCG.L	6	(–21, –11, 73)	2.51
PreCG.R	6	(37, –19, 69)	–2.27

BA, Brodmann area; MNI, Montreal Neurologic Institute; ITG.R, right inferior temporal gyrus; ORBinf.R, right orbital part of Inferior frontal gyrus; ORBmid.L, left orbital part of middle frontal gyrus; ORBsup.L, left orbital part of superior frontal gyrus; Caudate.L, left caudate; ACC.L left anterior cingulate cortex; ACC.R, right anterior cingulate cortex; IFGtriang.L, left triangular part of inferior frontal gyrus; MCC.L, left middle cingulate cortex; MCC.R right middle cingulate cortex; IPL.L, left inferior parietal lobule; Rectus.L, left rectus; Rectus.R, right rectus; SFG.R, right superior frontal gyrus; PreCG.R, right precentral gyrus; Putamen.R, right putamen; TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; SFG.L, left superior frontal gyrus; PreCG.L, left precentral gyrus.

Table 3 Brain regions showing overall fALFF differences between right Bell's palsy and healthy control groups (Z values, mean ± SD)

Groups	Brain regions											
	ITG.R	ORBinf.R	ORBmid.L	ORBsup.L	TPOsup.L	Caudate.L	ACC.L	ACC.R	IFGtriang.L	MCC.L	MCC.R	IPL.L
Right palsy	0.11±0.08	0.11±0.08	0.23±0.14	0.09±0.13	0.23±0.15	0.18±0.13	0.18±0.23	0.21±0.12	0.18±0.14	0.13±0.11	0.21±0.13	0.26±0.12
Healthy controls	0.09±0.08	0.09±0.07	0.17±0.08	0.05±0.12	0.22±0.12	0.16±0.09	0.12±0.17	0.14±0.08	0.16±0.13	0.08±0.05	0.16±0.09	0.26±0.09
t values	0.77	0.25	1.31	0.73	0.52	0.50	0.65	0.95	0.33	1.58	0.97	−0.17
P values	0.45	0.80	0.20	0.47	0.60	0.62	0.52	0.35	0.74	0.12	0.34	0.66

ITG.R, right inferior temporal gyrus; ORBinf.R, right orbital part of inferior frontal gyrus; ORBmid.L, left orbital part of middle frontal gyrus; ORBsup.L, left orbital part of superior frontal gyrus; Caudate.L, left caudate; ACC.L, left anterior cingulate cortex; ACC.R, right anterior cingulate cortex; IFGtriang.L, left triangular part of inferior frontal gyrus; MCC.L, left middle cingulate cortex; MCC.R, right middle cingulate cortex; IPL.L, left inferior parietal lobule.

inferior temporal gyrus (ITG), right orbital part of inferior frontal gyrus (ORBinf), left orbital part of the middle frontal gyrus (ORBmid), left orbital part of the superior frontal gyrus (SFG) (ORBsup), left temporal pole of the superior temporal gyrus (TPOsup), left caudate, bilateral anterior cingulate cortex (ACC), left triangular part of the inferior frontal gyrus (IFGtriang), bilateral MCC, and left inferior parietal gyrus (IPL) (*Table 2*).

Comparing the right palsy group with the healthy controls group, the means of the overall inter-regional FC of each brain region with other regions showed no significant differences (*Table 3*). In the right palsy group, the brain regions pairs with enhanced functional connectivities were the right ITG and orbital part of inferior frontal gyrus (P<0.05); right ITG and left MCC (P<0.05); left ORBmid and bilateral anterior cingulate cortex (P<0.05 and P<0.01); left caudate and bilateral anterior cingulate cortex (P<0.05); left and right MCC (P<0.01), and left MCC and inferior parietal gyrus (P<0.01). Also, the only region pair with decreased FC was the right ITG and left orbital part of middle frontal gyrus (P<0.01) (*Figure 1* , *Table S1*).

Differences between the left palsy and healthy control groups

The left palsy group showed significantly increased fALFF, compared with the healthy controls, in the left and right rectus, left orbital part of the SFG, right orbital part of middle frontal gyrus, right SFG, right precentral gyrus (PreCG), and right putamen (*Table 2*).

Comparing the left palsy group with the healthy controls, the means of the overall inter-regional functional connectivities of each brain region with other regions showed no significant differences (*Table 4*). In the left facial palsy group, the brain regions pairs with enhanced FC were the left and right rectus (P<0.05); left orbital part of SFG and right PreCG (P<0.01); right orbital part of middle frontal gyrus and SFG (P<0.05); right orbital part of middle frontal gyrus and PreCG (P<0.01); right SFG and PreCG (P<0.01), and right PreCG and putamen (P<0.05) (*Figure 1B*, *Table S2*).

Differences between the right and left palsy groups

The right Bell's palsy group showed significantly increased fALFF values, compared with the left palsy group, in the left temporal pole of the TPOsup, right supramarginal gyrus (SMG), bilateral MCC, left SFG, and left PreCG, and significantly decreased fALFF values in the right SFG and PreCG (*Table 2*, *Figure 2*).

The mean overall inter-regional functional connectivities of each brain region showed significant differences between the right and left palsy groups. Increased functional connectivities in the right palsy group were observed in the right SMG (P<0.01), bilateral SFG (P<0.05), and left PreCG (P<0.01) (*Table 5*, *Figure 3*).

Compared with that of the left palsy group, the region pairs in the right palsy group showing increased functional connectivities were the left temporal pole of the TPOsup and right SMG (P<0.05), left temporal pole of the TPOsup and MCC (P<0.05), left temporal pole of the TPOsup and PreCG (P<0.05), right SMG and SFG (P<0.05), MCC and left PreCG (P<0.05), left and right SFG (P<0.05), and right SFG and left PreCG (P<0.05) (*Figure 1C*, *Table S3*).

Correlation analysis

In the right palsy group, the FC of brain region pairs that showed a negative correlation with the TFGS score was the left temporal pole of the TPOsup and PreCG (P<0.05), while the right SFG and left PreCG showed a positive correlation (P<0.01).

In the left palsy group, the functional connectivities of the

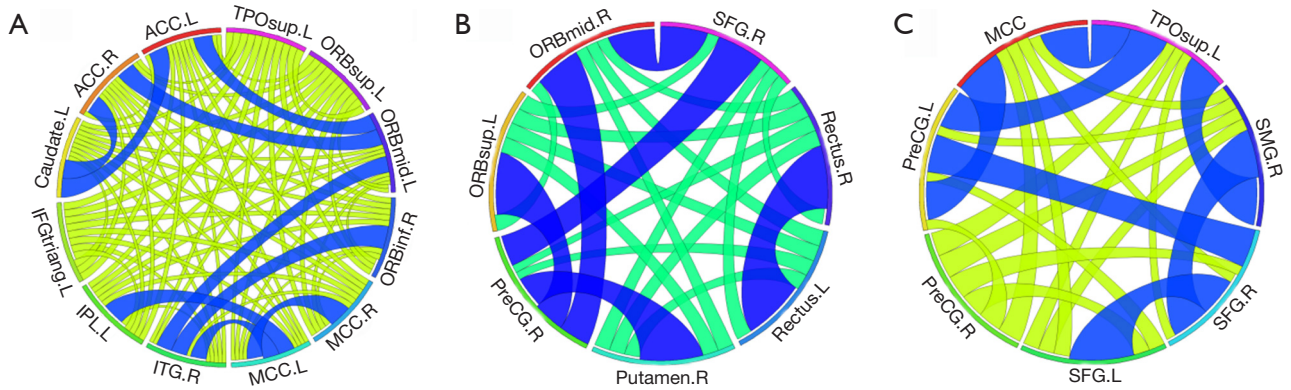

Figure 1 Comparison in functional connectivity of paired brain regions between every two groups. (A) Between right palsy and healthy control groups, the paired brain regions with abnormal functional connectivities were the right ITG and ORBinf, right ITG and left ORBmid, right ITG and left MCC, left ORBmid and ACC, left ORBmid and right ACC, left Caudate and ACC, left Caudate.L and right ACC, left and right MCC, left MCC and IPL. (B) Between left palsy and healthy control groups, the paired brain regions with abnormal functional connectivities were left and right rectus left ORBsup and right PreCG, right ORBmid and SFG, right ORBmid and PreCG, right SFG and PreCG, right PreCG and putamen. (C) Between right and left palsy groups, the paired brain regions with different functional connectivities were left TPOsup and right SMG left TPOsup and MCC, left TPOsup and left PreCG, right SMG and SFG, MCC and PreCG, left and right SFG, right SFG and left PreCG. ITG.R, right inferior temporal gyrus; ORBinf.R, right orbital part of inferior frontal gyrus; ORBmid.L, left orbital part of middle frontal gyrus; ORBsup.L, left orbital part of superior frontal gyrus; Caudate.L, left caudate; ACC.L, left anterior cingulate cortex; ACC.R, right anterior cingulate cortex; IFGtriang.L, left triangular part of inferior frontal gyrus; MCC.L, left middle cingulate cortex; MCC.R, right middle cingulate cortex; IPL.L, left inferior parietal lobule; Rectus.L, left rectus; Rectus.R, right rectus; ORBmid.R, right orbital part of middle frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.R, right precentral gyrus; Putamen.R, right putamen; TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; SFG.L, left superior frontal gyrus; PreCG.L, left precentral gyrus.

Table 4 Brain regions showing overall fALFF differences between left Bell's palsy and healthy control groups (Z values, mean ± SD)

Groups	Brain regions						
	Rectus.L	Rectus.R	ORBsup.L	ORBmid.R	SFG.R	PreCG.R	Putamen.R
Left palsy	0.39±0.26	0.37±0.16	0.39±0.23	0.24±0.13	0.17±0.12	0.18±0.15	0.11±0.05
Healthy controls	0.35±0.15	0.35±0.13	0.35±0.28	0.20±0.16	0.09±0.05	0.05±0.15	0.09±0.04
t values	0.29	0.29	0.45	0.66	1.49	1.45	0.81
P values	0.77	0.81	0.66	0.52	0.17	0.17	0.43

Rectus.L, left rectus; Rectus.R, right rectus; ORBsup.L, left orbital part of superior frontal gyrus; ORBmid.R, right orbital part of middle frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.R, right precentral gyrus; Putamen.R, right putamen.

brain region pairs showing a negative correlation with the TFGS were the left temporal pole of the TPOsup and right SMG (P<0.01), right SMG and SFG (P<0.01) (*Table S4*, *Figure 4*).

Discussion

We identified different brain functional remodeling mechanisms driven by right or left facial nerve efferent dysfunction in unilateral Bell's palsy. Compared with the healthy controls, the right palsy group showed significantly increased fALFF values in the right ITG, right ORBinf, left orbital part of middle frontal gyrus, and orbital part of SFG, bilateral cingulate cortex, and left triangular part of inferior frontal gyrus. These are all related to emotion control, including depression, anxiety, and other negative states (30-32).

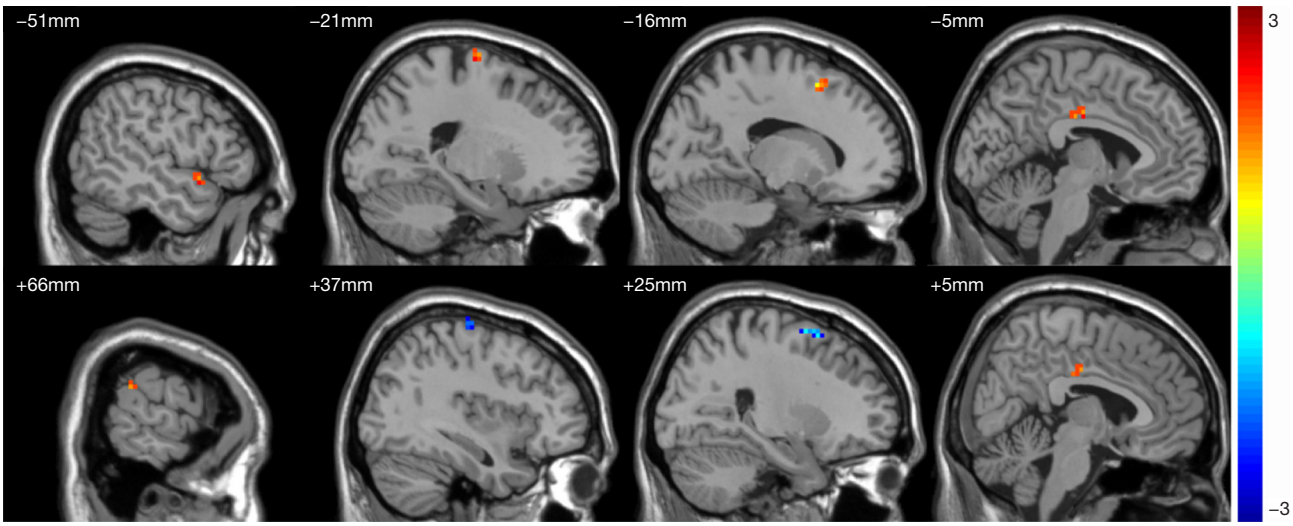

Figure 2 Brain regions showed fALFF differences between right and left palsy groups with post hoc *t*-test. Compared with the left Bell's palsy group, the right Bell's palsy group showed significantly increased fALFF values in the TPOsup.L, SMG.R, bilateral MCC, SFG.L, and PreCG.L, and significantly decreased fALFF values in the SFG.R and PreCG.R. TPOsup.L, left temporal pole of superior temporal gyrus, SMG.R, right supramarginal; MCC, middle cingulate cortex; SFG.L, left superior frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus; PreCG.R, right precentral gyrus.

Table 5 Brain regions showing overall fALFF differences between right and left Bell's palsy groups (Z values, mean ± SD)

Groups	Brain regions						
	TPOsup.L	SMG.R	MCC	SFG.L	SFG.R	PreCG.L	PreCG.R
Right palsy	0.27±0.19	0.19±0.11	0.13±0.12	0.18±0.11	0.22±0.13	0.22±0.12	0.17±0.13
Left palsy	0.19±0.11	0.12±0.79	0.08±0.14	0.13±0.10	0.15±0.09	0.12±0.09	0.15±0.13
t values	1.92	2.976	1.396	2.17	2.633	3.651	0.469
P values	0.059	0.004	0.167	0.034	0.011	0.001	0.641

TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; MCC, middle cingulate cortex; SFG.L, left superior frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus; PreCG.R, right precentral gyrus.

Some of these regions were also identified in the left palsy group. Furthermore, compared with the healthy controls, only the right palsy group showed increased fALFF values in the left TPOsup and IPL, involved in emotion perception and sensory (neural?) transmission (33,34). Also, the left caudate nucleus, identified in the right palsy group, is associated to motor function (35), while the left palsy group showed increased fALFF values in the right SFG, PreCG, and putamen, involved in the remodeling of the motor network (36). These differences suggest that the bilaterally different brain functional alterations derive from asymmetrical compensation in the left and right hemispheres (37). However, the mean overall inter-regional FC of each region showed no significant differences in either the right or left palsy groups compared with the healthy controls. This indicates that the brain functional activities in patients with facial palsy serve mainly to compensate for the damaged function, thereby maintaining the balance of the overall connectivity strength among these related functional regions. The brain region pairs with enhanced functional connectivities in the right palsy group compared with healthy controls were mainly related to emotion processing and perception functions; on the other hand, the left palsy group showed brain region pairs with enhanced

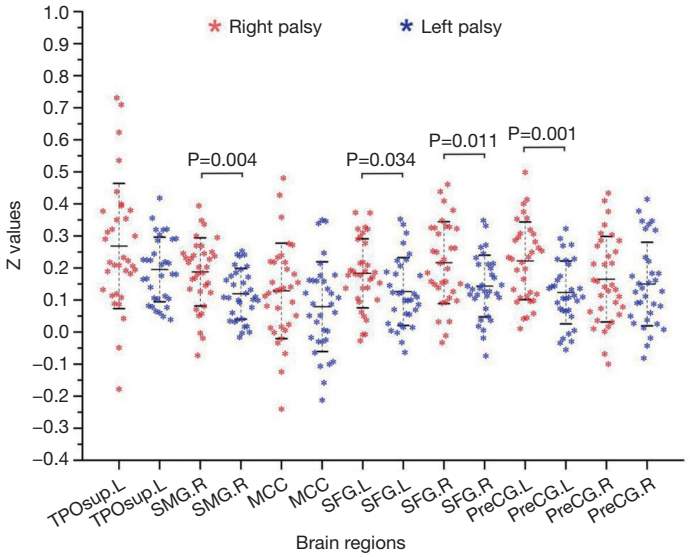

Figure 3 Comparisons in the overall functional connectivity of each paired brain regions with other regions between right and left Bell's palsy patient groups. The right Bell's palsy group showed significantly increased functional connectivities were observed in the right SMG, bilateral SFG, and left PreCG. TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; MCC, middle cingulate cortex; SFG.L, left superior frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus; PreCG.R, right precentral gyrus.

FC mainly involved in motor function remodeling. These regions with altered FC further highlight the differences in functional reorganization activities, mainly involving the emotional processes network in the right palsy group, and motor-related functional integration in the left palsy group, compared to the healthy controls. We speculate that psychological stress and negative emotions are heightened to different degrees in patients with bilateral Bell's palsy, because of their involuntary abnormal facial expressions and movements (30).

Compared with the results of the left palsy group, the right palsy group showed significantly increased fALFF values in the left temporal pole of the TPOsup, right SMG, bilateral MCC, left SFG, and left PreCG, and decreased fALFF in the right SFG and PreCG. Among these regions, the cingulate cortex is associated with emotional processing and involved in depression and anxiety (25,31,32,38); abnormal function in patients with Bell's palsy in this region has also been found by previous studies (37). This bilateral difference probably reflects different mechanisms of functional integration of emotions in patients with different side palsy (31). Compared with the results of the left Bell's palsy group, the right Bell's palsy group showed decreased fALFF values in the right SFG and PreCG, involved in the remodeling of the motor network (39). This indicates that motor function reintegration in patients with left and right facial palsy is different.

Interestingly, the right palsy group showed increased overall FC in the right SMG, bilateral SFG, and left PreCG compared with that of the left palsy group. Most of these regions are involved in the functional integration of motor and sensory transmission. Also, the SFG is related to self-awareness and laughter and is known as an essential gray matter nucleus with reported abnormalities in patients with Bell's palsy (22,23,36). Compared with the results of left Bell's palsy group, the right Bell's palsy groups showed increased fALFF values in the left temporal pole of the TPOsup and right SMG, which play vital roles in sensory transmission (33,34,40). This finding suggests that afferent nerve function is enhanced in the brains of patients with right early facial palsy, in agreement with earlier findings (28,41). This bilaterally different sensory reintegration mechanism probably derives from asymmetrical compensation in the bilateral hemispheres (37).

Furthermore, the region pairs with lower FC in the left palsy group highlighted the differences in the functional reorganization activities involved in emotional processes, motor networks and sensory transmission functions (24).

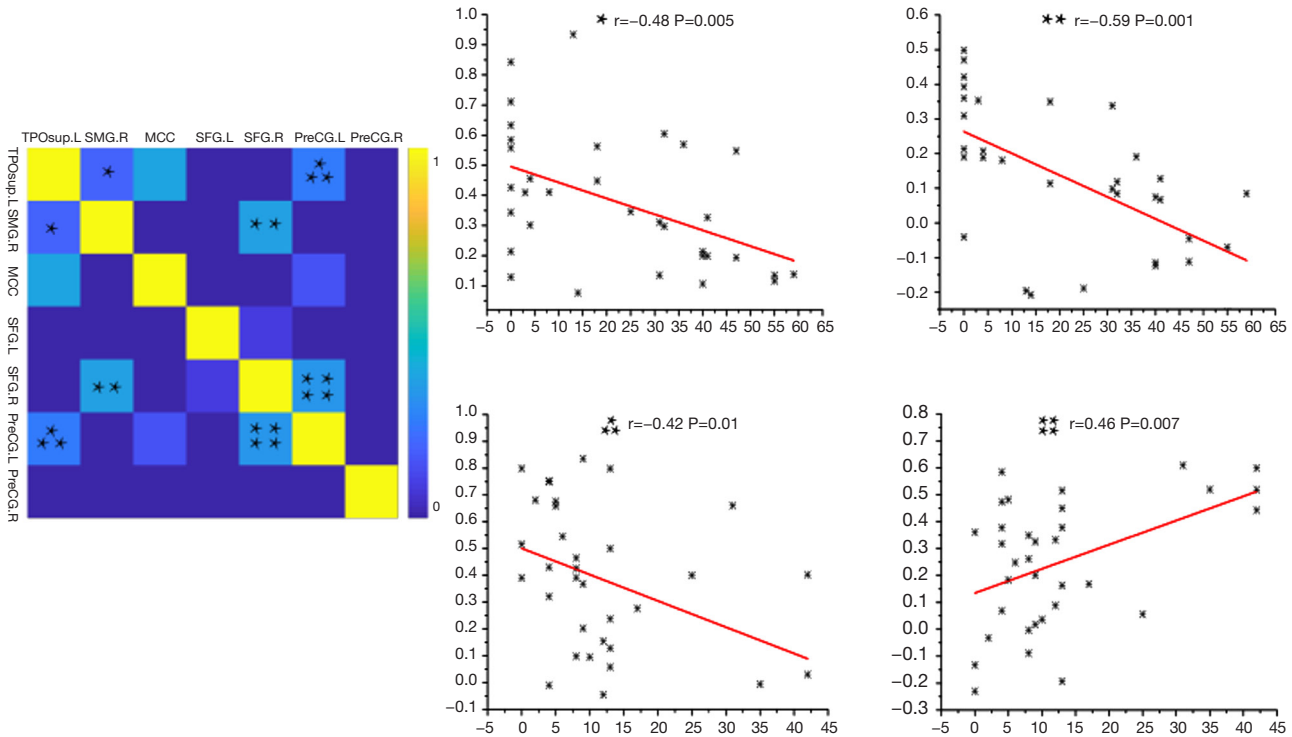

Figure 4 Correlation analysis in patients with left and right Bell's palsy. The left matrix diagram showed the paired brain regions with an inter-group difference. The paired brain regions that showed a negative correlation in the left Bell's palsy were the left TPOsup and right SMG (*), and right SMG and SFG (**). The paired brain regions that showed a negative correlation in the right Bell's palsy were left TPOsup and left PreCG (***), and positive correlation in the right SFG and left PreCG (****). TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; MCC, middle cingulate cortex; SFG.L, left superior frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus; PreCG.R, right precentral gyrus.

We also found that all the altered functional connectivities of region pairs in the right palsy group were significantly stronger than those in the left palsy group, suggesting a higher-level regulation of the dysfunction or damage in the early palsy stage (37). The exact remodeling mechanism remains unclear in the recovery stage, and further investigation is warranted.

The brain region pairs showing a negative correlation with the TFGS scores in patients with right facial palsy were the left temporal pole of TPOsup and left PreCG, and right SFG and left PreCG. On the other hand, the brain region pairs showing negative correlations with the TFGS scores in patients with left facial palsy were the left temporal pole of the TPOsup and right SMG, and right SMG and right SFG. Since the functional integration of most of these regions is related to sensory transmission and, to a lesser extent, to motor regulation (38), we speculate that the increase of motor regulation accompanies the increase of disease severity and that sensory transmission changes in patients with early facial palsy are related to disease severity. Thus, exercise rehabilitation therapy, which could increase facial muscles stimulation and nerve transmission actions, should be given more prominence in the treatment of patients with facial palsy, as was also suggested in previous studies (42,43).

This study has some limitations. Because of the difficulty in performing imaging examinations in patients with facial paralysis in the early stage, the sample size was relatively small, and we did not conduct follow-up or dynamic observations. Besides, since we only focused on local FC changes of selected regions, our study could not show inter-cortical connectivity changes in the whole brain. In a future study, the number of cases will be increased so that patients can be stratified by disease stage, and more comprehensive

network analysis will be performed.

Conclusions

Brain reintegration mechanisms appear to be differently driven by right or left facial nerve efferent dysfunction in patients with Bell's palsy. These differences probably derive from the asymmetrical compensation mechanisms employed by the bilateral hemispheres. The severity of the disease showed different associations with altered FC in some brain regions of the palsy patients. However, further study is needed to reveal the exact mechanisms underlying functional reintegration following Bell's palsy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by The Ethics Committee of our hospital and written informed consent was obtained from all patients.

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Supplementary

Table S1 Difference of functional connectivity in paired-regions between right Bell's palsy and healthy control groups (Z values, mean ± SD)

Two brain regions	Right facial palsy	Healthy controls	t values	P values
ITG.R/ORBinf.R	0.2±0.26	0.07±0.18	2.12	0.04
ITG.R/ORBmid.L	0.01±0.18	0.21±0.17	−4.05	<0.001
ITG.R/ORBsup.L	0.3±0.33	0.2±0.16	1.44	0.16
ITG.R/TPOsup.L	0.12±0.31	0.1±0.14	0.29	0.77
ITG.R/Caudate.L	0.06±0.17	0.09±0.18	−0.43	0.66
ITG.R/ACC.L	0.02±0.24	0.01±0.16	0.29	0.77
ITG.R/ACC.R	0.15±0.26	0.08±0.21	1.06	0.29
ITG.R/IFGtriang.L	0.23±0.29	0.19±0.19	0.54	0.59
ITG.R/MCC.L	0.05±0.15	0.01±0.21	2.05	0.04
ITG.R/MCC.R	0.13±0.22	0.08±0.19	0.98	0.33
ITG.R/IPL.L	0.05±0.17	0.07±0.09	−0.75	0.46
ORBinf.R/ORBmid.L	0.16±0.18	0.09±0.18	1.55	0.13
ORBinf.R/ORBsup.L	−0.03±0.19	−0.06±0.13	0.69	0.49
ORBinf.R/TPOsup.L	0.14±0.3	0.18±0.18	−0.71	0.48
ORBinf.R/Caudate.L	0.16±0.21	0.15±0.15	0.18	0.85
ORBinf.R/ACC.L	0.18±0.19	0.18±0.15	−0.08	0.94
ORBinf.R/ACC.R	0.25±0.24	0.26±0.19	−0.05	0.96
ORBinf.R/IFGtriang.L	0.06±0.22	0.08±0.2	−0.35	0.73
ORBinf.R/MCC.L	0.09±0.23	0.05±0.17	0.71	0.48
ORBinf.R/MCC.R	0.2±0.26	0.17±0.19	0.48	0.63
ORBinf.R/IPL.L	0.01±0.18	0.02±0.16	−0.14	0.88
ORBmid.L/ORBsup.L	0.3±0.45	0.26±0.29	0.41	0.68
ORBmid.L/TPOsup.L	0.31±0.22	0.23±0.25	1.32	0.19
ORBmid.L/Caudate.L	0.28±0.24	0.23±0.16	0.87	0.39
ORBmid.L/ACC.L	0.47±0.45	0.21±0.29	2.51	0.02
ORBmid.L/ACC.R	0.45±0.34	0.14±0.23	3.87	<0.001
ORBmid.L/IFGtriang.L	0.25±0.26	0.23±0.17	0.39	0.69
ORBmid.L/MCC.L	0.07±0.21	0.03±0.16	0.74	0.46
ORBmid.L/MCC.R	0.17±0.23	0.2±0.2	−0.54	0.59
ORBmid.L/IPL.L	0.11±0.22	0.18±0.14	−1.38	0.17
ORBsup.L/ITG.R	0.13±0.24	0.09±0.2	0.54	0.59
ORBsup.L/Caudate.L	0.04±0.21	0.02±0.26	0.46	0.65
ORBsup.L/ACC.L	−0.09±0.4	−0.15±0.26	0.64	0.52
ORBsup.L/ACC.R	−0.04±0.37	−0.12±0.28	0.88	0.38
ORBsup.L/IFGtriang.L	0.24±0.21	0.2±0.17	0.67	0.50
ORBsup.L/MCC.L	0.03±0.22	0.01±0.17	0.38	0.69
ORBsup.L/MCC.R	0.12±0.22	0.04±0.12	1.68	0.09
ORBsup.L/IPL.L	0.05±0.18	0.09±0.14	−1.05	0.29
TPOsup.L/Caudate.L	0.25±0.21	0.28±0.2	−0.55	0.58
TPOsup.L/ACC.L	0.13±0.25	0.13±0.16	−0.09	0.92
TPOsup.L/ACC.R	0.18±0.28	0.13±0.17	0.72	0.46
TPOsup.L/IFGtriang.L	0.55±0.35	0.46±0.29	1.00	0.32
TPOsup.L/MCC.L	0.26±0.28	0.14±0.16	1.85	0.07
TPOsup.L/MCC.R	0.39±0.22	0.32±0.23	1.18	0.24
TPOsup.L/IPL.L	0.35±0.21	0.37±0.18	−0.31	0.76
Caudate.L/ACC.L	0.4±0.25	0.25±0.18	2.49	0.02
Caudate.L/ACC.R	0.39±0.23	0.27±0.2	2.09	0.04
Caudate.L/IFGtriang.L	0.2±0.15	0.18±0.21	0.36	0.72
Caudate.L/MCC.L	0.08±0.17	0.06±0.14	0.34	0.74
Caudate.L/MCC.R	0.19±0.15	0.24±0.22	−0.76	0.45
Caudate.L/IPL.L	0.14±0.2	0.16±0.13	−0.28	0.78
ACC.L/ACC.R	0.7±0.3	0.58±0.22	1.58	0.11
ACC.L/IFGtriang.L	0.1±0.2	0.08±0.16	0.43	0.66
ACC.L/MCC.L	0.05±0.23	0.01±0.15	0.77	0.44
ACC.L/MCC.R	0.14±0.19	0.12±0.19	0.43	0.67
ACC.L/IPL.L	0.01±0.2	0.03±0.13	−0.39	0.69
ACC.R/IFGtriang.L	0.14±0.26	0.13±0.16	0.13	0.89
ACC.R/MCC.L	0.1±0.23	0.01±0.2	1.49	0.14
ACC.R/MCC.R	0.24±0.2	0.17±0.19	1.16	0.25
ACC.R/IPL.L	0.01±0.21	−0.01±0.13	0.30	0.76
IFGtriang.L/MCC.L	0.06±0.25	−0.01±0.18	1.11	0.27
IFGtriang.L/MCC.R	0.17±0.21	0.15±0.16	0.45	0.65
IFGtriang.L/IPL.L	0.18±0.21	0.27±0.18	−1.60	0.11
MCC.L/MCC.R	0.48±0.25	0.26±0.24	3.22	0.002
MCC.L/IPL.L	0.28±0.2	0.13±0.16	2.82	0.006
MCC.R/IPL.L	0.25±0.23	0.23±0.16	0.49	0.63

ITG.R, right inferior temporal gyrus; ORBinf.R, right orbital part of inferior frontal gyrus; ORBmid.L, left orbital part of middle frontal gyrus; ORBsup.L, left orbital part of superior frontal gyrus; Caudate.L, left caudate; ACC.L, left anterior cingulate cortex; ACC.R, right anterior cingulate cortex; IFGtriang.L, left triangular part of inferior frontal gyrus; MCC.L, left middle cingulate cortex; MCC.R, right middle cingulate cortex; IPL.L, left inferior parietal lobule.

Table S2 Difference of functional connectivity in paired-regions between left Bell's palsy and healthy control groups (Z values, mean ± SD)

Two brain regions	Left facial palsy	Healthy controls	t values	P values
Rectus.L/Rectus.R	1.06±0.34	0.88±0.27	2.148	0.037
Rectus.L/ORBsup.L	0.94±0.52	0.82±0.3	0.988	0.328
Rectus.L/ORBmid.R	0.39±0.33	0.36±0.24	0.412	0.682
Rectus.L/SFG.R	0.08±0.22	0.04±0.2	0.791	0.433
Rectus.L/PreCG.R	0.08±0.23	–0.01±0.12	1.66	0.103
Rectus.L/Putamen.R	0.11±0.14	0.11±0.15	–0.205	0.838
Rectus.R/ORBsup.L	0.85±0.47	0.71±0.3	1.276	0.208
Rectus.R/ORBmid.R	0.4±0.35	0.22±0.13	0.155	0.877
Rectus.R/SFG.R	0.05±0.24	0.08±0.17	–0.567	0.574
Rectus.R/PreCG.R	0.1±0.25	0.23±0.11	0.941	0.351
Rectus.R/Putamen.R	0.08±0.2	0.1±0.14	–0.331	0.742
ORBsup.L/ORBmid.R	0.4±0.4	0.36±0.24	–0.331	0.742
ORBsup.L/SFG.R	0.15±0.22	0.04±0.18	1.934	0.059
ORBsup.L/PreCG.R	0.14±0.24	–0.04±0.14	3.238	0.002
ORBsup.L/Putamen.R	0.15±0.17	0.13±0.14	0.501	0.618
ORBmid.R/SFG.R	0.21±0.19	0.09±0.19	2.098	0.041
ORBmid.R/PreCG.R	0.23±0.29	0.04±0.15	2.986	0.004
ORBmid.R/Putamen.R	0.14±0.2	0.13±0.14	0.173	0.863
SFG.R/PreCG.R	0.53±0.25	0.32±0.23	3.107	0.003
SFG.R/Putamen.R	0.19±0.12	0.11±0.15	2	0.051
PreCG.R/Putamen.R	0.15±0.15	0.06±0.14	2.033	0.048

Rectus.L, left rectus; Rectus.R, right rectus; ORBsup.L, left orbital part of superior frontal gyrus; ORBmid.R, right orbital part of middle frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.R, right precentral gyrus; Putamen.R, right putamen.

Table S3 Difference of functional connectivity in paired-regions between right and left Bell's palsy groups (Z values, mean ± SD)

Paired brain regions	right controls	left facial palsy	t values	P values
TPOsup.L/SMG.R	0.52±0.26	0.38±0.23	2.313	0.031
TPOsup.L/MCC	0.23±0.34	0.07±0.24	2.679	0.012
TPOsup.L/SFG.L	0.21±0.22	0.14±0.18	0.956	0.344
TPOsup.L/SFG.R	0.29±0.23	0.25±0.14	0.804	0.426
TPOsup.L/PreCG.L	0.37±0.28	0.23±0.23	2.894	0.025
TPOsup.L/PreCG.R	0.26±0.29	0.30±0.27	–0.484	0.631
SMG.R/MCC	0.13±0.21	0.10±0.23	0.487	0.628
SMG.R/SFG.L	0.12±0.31	0.02±0.16	1.326	0.191
SMG.R/SFG.R	0.24±0.22	0.12±0.22	2.672	0.013
SMG.R/PreCG.L	0.18±0.23	0.08±0.21	1.508	0.139
SMG.R/PreCG.R	0.13±0.24	0.10±0.24	0.532	0.597
MCC/SFG.L	0.18±0.21	0.19±0.18	–0.094	0.926
MCC/SFG.R	0.13±0.25	0.07±0.29	0.836	0.408
MCC/PreCG.L	0.16±0.22	0.04±0.16	2.176	0.035
MCC/PreCG.R	0.11±0.24	0.08±0.22	0.427	0.671
SFG.L/SFG.R	0.48±0.27	0.32±0.27	2.007	0.041
SFG.L/PreCG.L	0.18±0.24	0.08±0.21	1.591	0.119
SFG.L/PreCG.R	0.09±0.21	0.15±0.19	–0.906	0.37
SFG.R/PreCG.L	0.24±0.25	0.13±0.16	2.614	0.016
SFG.R/PreCG.R	0.13±0.23	0.11±0.24	0.408	0.685
PreCG.L/PreCG.R	0.41±0.29	0.31±0.32	1.116	0.271

TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; MCC, middle cingulate cortex; SFG.L, left superior frontal gyrus; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus; PreCG.R, right precentral gyrus.

Table S4 Correlation analysis between TFGS scores and the functional connectivity in different paired brain regions

Group	Paired brain regions	r values	P values
Right facial palsy	TPOsup.L & PreCG.L	–0.42	0.01
	SFG.R& PreCG.L	0.46	0.007
Left facial palsy	TPOsup.L & SMG.R	–0.48	0.005
	SMG.R & SFG.R	–0.59	0.001

TPOsup.L, left temporal pole of superior temporal gyrus; SMG.R, right supramarginal; SFG.R, right superior frontal gyrus; PreCG.L, left precentral gyrus.