

## Research Article

# Motor Control Deficits in Facial Synkinesis Patients: Neuroimaging Evidences of Cerebral Cortex Involvement

Jia-jia Wu <sup>1</sup>, Ye-chen Lu <sup>2</sup>, Mou-xiong Zheng <sup>1,3</sup>, Xu-yun Hua<sup>1,3</sup>, Jian-guang Xu <sup>1,2</sup>, Wei Ding <sup>4</sup> and Chun-lei Shan<sup>1,2</sup>

<sup>1</sup>Center of Rehabilitation Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

<sup>2</sup>School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China

<sup>3</sup>Department of Trauma and Orthopedics, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

<sup>4</sup>Department of Plastic and Reconstructive Surgery, Shanghai Ninth People Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

Correspondence should be addressed to Jian-guang Xu; [jianguangxu@fudan.edu.cn](mailto:jianguangxu@fudan.edu.cn) and Wei Ding; [drdingwei@outlook.com](mailto:drdingwei@outlook.com)

Received 29 December 2018; Revised 5 February 2019; Accepted 3 March 2019; Published 27 March 2019

Academic Editor: Carlo Cavaliere

Copyright © 2019 Jia-jia Wu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Objective.** Facial synkinesis is a severe sequelae of facial nerve malfunction. Once the synkinesis is established, it is extremely difficult for patients to recover. Given that the restoration of motor or sensory function after peripheral nerve injury was closely related with cortical plasticity, we investigated cortical plasticity in facial synkinesis patients by the frequency-specific data which remains largely uncharacterized. **Materials and Methods.** Resting-state fMRI was conducted in 20 facial synkinesis patients and 19 healthy controls, and the amplitude of low-frequency fluctuation (ALFF) in five different frequency bands (slow-6: 0-0.01 Hz; slow-5: 0.01-0.027 Hz; slow-4: 0.027-0.073 Hz; slow-3: 0.073-0.167 Hz; and slow-2: 0.167-0.25 Hz) was calculated, respectively. And the relationship between ALFF and clinical outcomes was also analyzed. **Results.** Comparing with the healthy controls, facial synkinesis patients showed significantly different ALFF values, mainly in the sensorimotor areas. Furthermore, increased ALFF of the ipsilateral insula in the slow-6 band was significantly related with better facial nerve function. **Conclusion.** Increased ALFF values in the ipsilateral insula might reflect an abnormal state of hypercompensation in motor control of facial synkinesis patients. It provided valuable spatial information about the functionally aberrant regions, which implied the possible involvement of motor control system in facial synkinesis.

## 1. Introduction

Facial synkinesis, one of the most troublesome sequelae of facial nerve paralysis, is characterized by synchronous and involuntary contractions of the muscles during volitional facial movements [1, 2]. Currently, despite the improved surgical techniques coupled with the use of botulinum toxin A injection, the results of these remained far from satisfactory [3, 4]. In the past years, researchers demonstrated several possible mechanisms of facial synkinesis, including aberrant regeneration and mismatch of axons [1, 5], ephaptic transmission between neighboring axons [5], and over-acting of the facial nucleus in the pons [6]. However,

none of them has perfectly interpreted all the issues about facial synkinesis. In other words, the underlying pathological mechanism of facial synkinesis is still not clearly elucidated. In the recent years, emerging evidences showed that functional outcome of peripheral neuropathy was closely associated with both peripheral recovery and cortical adaptation [7]. After years of digging peripheral reasons of facial synkinesis, we speculate that brain plasticity is also responsible for the deficits of facial motor control. Therefore, the investigation of cortical plasticity derived from facial synkinesis is now an interesting and vital question.

In our previous studies, we investigated the cortical functional alterations in patients with unilateral facial

synkinesis using the task-designed fMRI [8, 9]. Results demonstrated that the distance of the representation sites during ipsilateral blinking and smiling tasks was decreased on the affected half face compared to the unaffected face in patients. And facial movements on either side performed by patients caused more intensive activation in the supplementary motor area on the contralateral side of the affected face than those on the unaffected side. Although we have successfully described alternation of activation in the primary sensorimotor area, higher order processing system, which also contributes to the complex motor control, is still out of our vision. The regulatory effect on facial motor control from other brain regions could not be ignored. There is a possibility that the facial synkinesis is not only a single problem of motor execution but also a complex problem concerning motor regulation or motor control. A resting-state fMRI study indicated that patients with facial palsy showed decreased connectivity mainly in areas responsible for sensorimotor integration and supervision, and the decreased connectivity between SII and the insula significantly correlated to the severity of the facial palsy [10]. Considering the persistency of facial nerve malfunction, some resting-state fMRI measurements such as amplitude of low-frequency fluctuation (ALFF) might provide more valuable information of the brain status.

ALFF is an effective measurement for detecting low-frequency oscillation (LFO) activities at resting state, which has been widely applied in functional neuroimaging [11]. Recent researches have indicated that neuronal oscillations are distributed linearly on the natural logarithmic scale and different spatial distributions of ALFF in distinct frequency bands may result from the neuronal input selection and plasticity [12–15]. However, the combination of every different band of ALFF results in insignificance of statistical analysis. In this study, the low-frequency fluctuation range is subdivided into five frequency bands: slow-6 (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.25 Hz) [15]. And the power of different frequency bands varied among different anatomical and functional properties of the brain. With this method, we aimed to investigate the spontaneous changes of neural activity in facial synkinesis patients by the frequency-specific data, which would lead to a better understanding of facial synkinesis-related neuroplasticity. Furthermore, the relationship between ALFF and clinical outcomes was also analyzed. We also attempted to address the most correlated region and its frequency band, which might offer useful localization advices for researches of cortical interventions.

## 2. Methods and Materials

**2.1. Participants.** A total of 20 facial synkinesis patients and 19 healthy controls were enrolled in this study. Diagnosis of facial synkinesis was made by two experienced plastic surgeons from the Department of Plastic Surgery at The Ninth People’s Hospital, School of Medicine, Shanghai Jiaotong University, before the fMRI scans. We recruited patients with unilateral facial synkinesis, absence of nerve

transposition, and with no other medical or psychological disorders. Participants were excluded if the facial palsy was recurrent or with concurrent peripheral neuropathy and with contraindications to investigation by MRI. The study was approved by the local ethics committee, and all patients provided written informed consent according to the Helsinki Declaration.

**2.2. Clinical Assessments.** The Sunnybrook facial grading system was applied for the clinical assessment of peripheral facial nerve palsy [16]. This grading system measures three components including facial resting symmetry, symmetry of voluntary movement, and synkinesis. The score ranges from 0 to 100, with higher score indicating better facial nerve function. In this study, the assessment of facial nerve function was directly evaluated by two experienced physicians after the fMRI scan.

**2.3. fMRI Acquisition.** The duration from facial palsy to fMRI scanning is provided in Table 1. The fMRI data were collected using a 3.0T MRI scanner (MR750, GE Healthcare, USA). Participants were instructed to lie still and rest quietly and their heads were immobilized with foam pads. The resting-state fMRI data were obtained with a single-shot gradient-recalled EPI sequence with the following parameters: interleaved scanning order, slice number = 43, matrix size =  $64 \times 64$ , FOV =  $220 \times 220$  mm, TR = 2000 ms, flip angle =  $90^\circ$ , slice thickness = 3.2 mm, gap = 0 (voxel size  $3.4 \times 3.4 \times 3.2$  mm<sup>3</sup>), and number of acquisitions = 240.

**2.4. Data Preprocessing.** fMRI data were preprocessed in accordance with pipelines recommended by Yu-Feng et al. [17] using the Statistical Parametric Mapping 8 toolbox (<http://www.fil.ion.ucl.ac.uk/spm/>) on MATLAB 2014a platform. The brain images of right-sided facial synkinesis patients were flipped along the  $y$ -axis prior to analysis to ensure the consistency of sides among patients. The first 10 images of each functional session were removed for the signal equilibrium. The acquired functional images were preprocessed as follows: (1) slice scan time correction, (2) head movement correction (the head movements were all less than 2.5 mm or 2.5 degrees in any direction), (3) spatial normalization of the functional images via standard EPI template, (4) regressing nuisance variables including the white matter and cerebral spinal fluid blood oxygen level-dependent (BOLD) signal and effects of head motion using six head motion profiles, (5) spatial smoothing using a Gaussian kernel of 4 mm full width at half maximum, and (6) removal of linear trends.

No temporal filtering during preprocessing assures that the entire frequency band below the Nyquist frequency (0.25 Hz) can be examined in subsequent analyses of ALFF.

**2.5. ALFF Measures in Different Frequency Bands.** Subsequent to data preprocessing, the time series for each voxel was transformed to the frequency domain using the fast Fourier transform. The power spectrum was obtained in different frequency bands at each voxel. The low-frequency range was subdivided into five bands as

TABLE 1: Demographic information of enrolled subjects.

Items	Facial synkinesis group ( $n = 20$ )	Healthy control group ( $n = 19$ )	$P$ value
Age	33.35 $\pm$ 6.97	33.21 $\pm$ 6.75	0.950 <sup>a</sup>
Gender	2 (female)/18 (male)	2 (female)/17 (male)	0.957 <sup>b</sup>
Duration	26.05 $\pm$ 14.20 m	—	—
Affected side	9 (right)/11 (left)	—	—
Sunnybrook scores	42.45 $\pm$ 19.24	—	—

<sup>a</sup>Two independent sample  $t$ -tests. <sup>b</sup>Chi-square test.

previously defined: slow-6 (0-0.01 Hz), slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.073 Hz), slow-3 (0.073-0.198 Hz), and slow-2 (0.198-0.25 Hz) [15].

As the power of a given frequency was proportional to the square of the amplitude of this frequency component, the square root of the power spectrum was calculated at each frequency. Then, the averaged square root (i.e., ALFF value) of the power spectrum in different frequency bands was calculated [18]. Finally, each individual's ALFF value was transformed to  $Z$  score to allow further comparison between groups.

**2.6. Statistical Analysis.** To investigate the effects of disease on different frequency bands, we performed an ANOVA (flexible factorial design,  $2 \times 5$ ) using the SPM8 software within a standard (Montreal Neurological Institute space) grey matter mask. The group was considered to be a between-subject factor with two levels (facial synkinesis patients vs. healthy controls). The frequency band was regarded as a correlated repeated measure factor with five levels. The interactions of group and frequency were considered as effects in the model. After the interaction effect analysis, significant clusters were generated within a binary mask. Further, post hoc two-sample  $t$ -tests were performed for group comparison of each frequency band within the previously generated mask. All significance tests were conducted at a false discovery rate (FDR) threshold of  $P = 0.05$ .

**2.7. Correlation Analysis.** The correlation between ALFF values of the ROIs in each frequency band and Sunnybrook scores was also analyzed. The ROIs for correlation analysis were extracted from the largest significant cluster revealed by post hoc  $t$ -tests between the two groups in each frequency band. Spearman's correlative analyses were used to examine relationships between abnormal ALFF values and Sunnybrook scores in facial synkinesis patients using SPSS 22 software (SPSS Inc., Chicago, IL).

### 3. Results

**3.1. Clinical Characteristics.** There were no significant differences in age or gender between the facial synkinesis patients and the healthy controls. Among the facial synkinesis patients, 9 were with right-sided palsy and 11 were left-sided. The duration of facial palsy from onset to fMRI scanning was 26.05  $\pm$  14.20 months. All patients showed a unilateral loss of facial function, with mean Sunnybrook score of 42.45  $\pm$  19.24 points (Table 1).

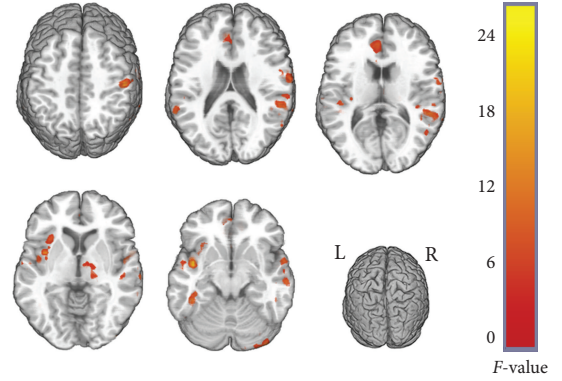


FIGURE 1: Interaction effects of group  $\times$  frequency by a two-way ANOVA. The red-yellow regions represent significant interaction between disease and frequency.

TABLE 2: Interaction effects of group  $\times$  frequency by a two-way ANOVA.

Brain regions	Cluster size	Cluster centroid (MNI)			$F$ value
		$x$	$y$	$z$	
Frontal_Med_Orbital_L	39	0	36	-12	24.4579
Insula_L	36	-42	3	-9	25.9851
Postcentral_R	36	51	-27	51	20.6439
Temporal_Sup_R	35	54	-39	15	15.8532
Cingulate_Ant_L	32	-3	36	24	12.3385
Insula_L	31	-30	21	6	9.2927
Temporal_Inf_L	24	-42	-39	-15	16.4087
Cerebellum_Crush1_R	18	39	-87	-33	21.6993
Temporal_Mid_R	18	60	-3	-18	15.6285
Postcentral_R	17	66	-12	21	13.1904
Orbital_frontal_med_R	16	15	48	-18	11.895
Thalamus_R	14	21	-21	6	12.5973
Orbital_frontal_post_L	13	-21	24	-18	11.873
Temporal_Pole_Mid_R	13	45	12	-30	10.9921
Temporal_Mid_R	12	69	-48	6	15.2749
Temporal_Sup_L	12	-57	-45	21	15.1745
Temporal_Pole_Sup_R	11	30	9	-24	20.7315
Temporal_Inf_L	11	-33	12	-39	18.3323

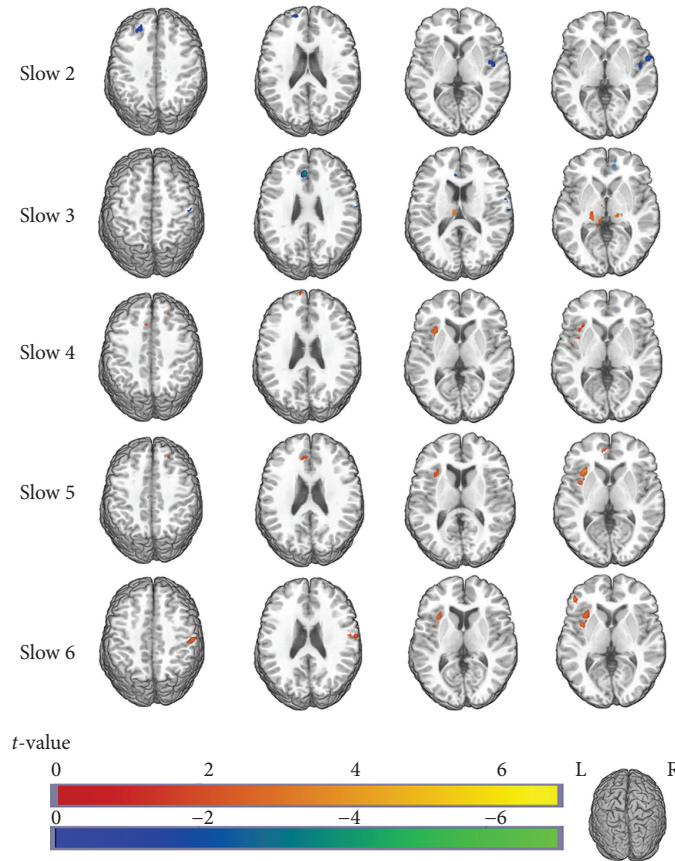


FIGURE 2: Difference in the amplitude of low-frequency fluctuation (ALFF) between facial synkinesis patients and healthy controls. Each row in the figure displays difference of ALFF between facial synkinesis patients and healthy controls in each of the five frequency bands. The warm tone represents signal of patients greater than healthy controls, while the cold tone represents signal of patients less than healthy controls.

### 3.2. ALFF Results

**3.2.1. Interaction Effects of Group  $\times$  Frequency Band.** Significant interaction effects of disease  $\times$  frequency were distributed over the left insula, right middle temporal cortex, left inferior temporal cortex, right cerebellum, bilateral superior temporal cortex, bilateral orbit frontal cortex, right postcentral cortex, right thalamus, and left anterior cingulate cortex (ACC) (Figure 1 and Table 2).

**3.2.2. Post hoc Two-Sample  $t$ -Tests between Groups.** To investigate differences between the two groups in each frequency band, further post hoc two-sample  $t$ -tests were performed (Figure 2 and Table 3).

In the slow-2 band, facial synkinesis patients exhibited significantly decreased ALFF values comparing with the healthy controls in the bilateral ACC, right insula, right cerebellum, right superior temporal cortex, left superior frontal cortex, right middle temporal cortex, right postcentral cortex, and right medial superior frontal gyrus.

In the slow-3 band, facial synkinesis patients showed significantly increased ALFF in the left hippocampus, left cerebellum, and bilateral thalamus and significantly decreased ALFF in the left ACC, right middle temporal cortex, right cerebellum, right postcentral cortex, and right orbit frontal cortex.

In the slow-4 band, facial synkinesis patients showed significantly increased ALFF in the right cerebellum, left insula, right superior temporal cortex, left hippocampus, left medial superior frontal cortex, and right superior frontal cortex and significantly decreased ALFF in the right orbit frontal cortex.

In the slow-5 band, facial synkinesis patients showed significantly increased ALFF in the left insula and left inferior temporal cortex, right superior frontal cortex, left ACC, and left hippocampus and significantly decreased ALFF in the right hippocampus.

In the slow-6 band, facial synkinesis patients showed significantly increased ALFF in the left insula, left inferior frontal cortex, left inferior temporal cortex, left middle temporal cortex, right postcentral cortex, left ACC, and right middle temporal cortex and significantly decreased ALFF in the right hippocampus, and left cerebellum.

**3.3. Clinical Correlation.** Significant correlation was found between the Sunnybrook scores and ALFF values in facial synkinesis patients for the cluster of the left insula in the slow-6 band ( $r = 0.584$ ,  $P = 0.007$ ). However, ALFF values of the other significantly different clusters between groups in the slow-2 to slow-5 bands (the right insula in the slow-2 band, the left thalamus in the slow-3 band, the left insula in

TABLE 3: Differences in ALFF between facial synkinesis patients and healthy controls in 5 frequency bands.

Brain regions	Cluster size	Cluster centroid(MNI)			<i>t</i> value	
		<i>x</i>	<i>y</i>	<i>z</i>		
Slow-2 band						
Facial synkinesis < healthy controls						
	Insula_R	32	48	-6	3	-3.4274
R	Temporal_Pole_Sup_	30	30	18	-27	-2.6361
	Cingulate_Ant_R	30	9	42	0	-3.3372
	Postcentral_R	27	51	-27	48	-3.3814
	Cerebelum_Crus1_R	25	39	-87	-33	-4.0931
	Temporal_Mid_R	22	60	-3	-18	-2.4222
R	Frontal_Sup_Medial_	21	6	36	42	-2.899
R	Temporal_Pole_Mid_	19	48	9	-30	-2.8583
	Frontal_Sup_L	16	-21	36	36	-2.6557
	Cingulate_Ant_L	12	-6	30	18	-3.1261
Slow-3 band						
Facial synkinesis > healthy controls						
	Thalamus_L	82	-18	-27	-3	2.8462
	Hippocampus_L	48	-21	-24	-9	4.9978
	Cerebelum_10_L	30	-21	-33	-45	4.8498
	Thalamus_R	11	12	-24	3	2.8505
Facial synkinesis < healthy controls						
Orbital_R	Frontal_Med_	42	12	48	-9	-2.7222
	Cingulate_Ant_L	22	-3	36	27	-3.8034
Crus1_R	Cerebelum_	22	39	-87	-33	-3.2934
	Temporal_Mid_R	10	60	-3	-21	-3.3251
	Postcentral_R	10	66	-15	15	-3.1111
Crus2_R	Cerebelum_	10	39	-75	-51	-2.7581
Slow-4 band						
Facial synkinesis > healthy controls						
	Insula_L	36	-27	12	-21	2.5823
	Hippocampus_L	16	-21	-24	-9	3.222
	Cerebelum_9_R	15	12	-48	-54	4.2794
Sup_R	Temporal_Pole_	15	30	9	-24	4.137
Medial_L	Frontal_Sup_	12	-9	66	9	3.6189
	Hippocampus_L	10	-18	-12	-12	3.9069
	Frontal_Sup_2_R	10	24	36	42	2.7278
Facial synkinesis < healthy controls						
Orbital_R	Frontal_Med_	10	12	42	-6	-2.3628

TABLE 3: Continued.

Brain regions	Cluster size	Cluster centroid(MNI)			<i>t</i> value	
		<i>x</i>	<i>y</i>	<i>z</i>		
Slow-5 band						
Facial synkinesis > healthy controls						
	Insula_L	43	-33	15	9	3.353
	Frontal_Sup_2_R	12	27	9	66	2.9628
	Cingulate_Ant_L	12	-3	33	-9	2.8405
	Temporal_Inf_L	11	-42	6	-42	3.2313
	Hippocampus_L	11	-21	-24	-9	2.6231
	Frontal_Sup_2_R	10	24	39	42	2.3045
Facial synkinesis < healthy controls						
	Hippocampus_R	15	33	-12	-15	-2.9439
Slow-6 band						
Facial synkinesis > healthy controls						
	Insula_L	61	-39	6	0	3.8307
	Postcentral_R	37	57	-21	45	3.3997
	Temporal_Pole_	28	-21	9	-36	2.6843
Mid_L	Cingulate_Ant_L	27	-3	39	18	3.3037
	Temporal_Inf_L	22	-42	6	-42	3.6417
	Frontal_Inf_	10	-48	39	3	3.9693
Triangle_L						
Facial synkinesis < healthy controls						
	Cerebelum_9_L	24	-9	-54	-51	-2.8445
	Hippocampus_R	15	30	-21	-15	-3.0374

the slow-4 band, and the left insula in the slow-5 band) failed to show significant correlation with the Sunnybrook scores (Figure 3).

## 4. Discussion

**4.1. Main Findings.** In the present study, we investigated frequency-specific ALFF alteration between facial synkinesis patients and healthy controls in the distribution of intrinsic brain hemodynamic oscillations across five frequency bands (slow-2 to slow-6). We also investigated the capability of the frequency-specific alterations in providing predictive information with the frequency-specific alterations. The main findings were concluded as follows: (1) a significant interaction effect of the group  $\times$  frequency band was observed mainly in the sensorimotor regions; (2) post hoc two-sample *t*-tests showed significant differences in ALFF between the two groups in each frequency band; and (3) in the slow-6 band, ALFF values of facial synkinesis patients' insula were most significantly related with facial synkinesis patients' Sunnybrook scores.

**4.2. Alterations of ALFF in Each Frequency Band.** ALFF was reported to describe the local spontaneous neuronal activity [19]. Previous studies of electroencephalography have demonstrated that LFO represented spontaneous neural activity which generated its rhythmic activity patterns through

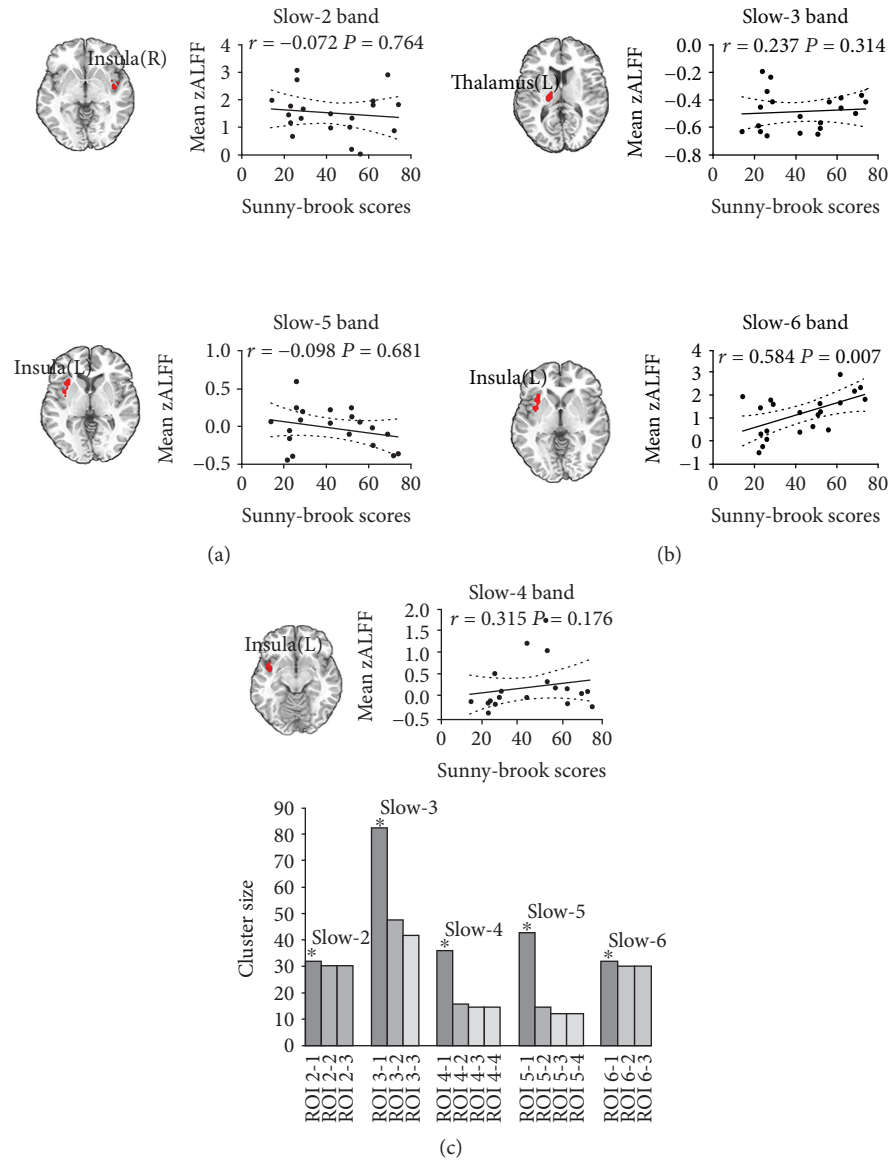


FIGURE 3: Spearman correlation analysis between Sunnybrook scores and ALFF values in five ROIs. The ROIs were extracted from the largest significant cluster revealed by post hoc  $t$ -tests between the two groups in each frequency band. The bar graph showed the significant clusters of different ALFF between facial synkinesis patients and healthy controls by a post hoc two-sample  $t$ -test in each frequency band. ROI 2-1: right insula; ROI 2-2: right superior temporal pole; ROI 2-3: right anterior cingulate cortex(ACC); ROI3-1: left thalamus; ROI3-2: left hippocampus; ROI3-3: right medial orbit frontal cortex; ROI4-1: left insula; ROI4-2: left hippocampus; ROI4-3: right cerebellum; ROI4-4: right superior temporal pole; ROI5-1: left insula; ROI5-2: right hippocampus; ROI5-3: right superior frontal gyrus; ROI5-4: left ACC; ROI6-1: left insula; ROI6-2: right postcentral gyrus; ROI6-3: left middle temporal pole.

information exchange with neighboring brain areas [15]. Most fMRI studies measured ALFF at a typical frequency range between 0.01 and 0.08 Hz which was thought to be physiologically meaningful [20, 21]. However, the fMRI scan objectively enabled possible detection of fluctuations over 0.1 Hz [21]. According to the Buzsáki framework, the full frequency range (0-0.25 Hz) was subdivided into five frequency bands (slow-2, slow-3, slow-4, slow-5, and slow-6 bands) [15]. Although the exact mechanism of different bands is still controversial, several researchers have tried to give some explanations of frequency-specific ALFF. The neurophysiological mechanisms that underlie oscillations within specific classes may be linked

to specific neurophysiological processes, including input selection, plasticity, binding, and consolidation [13–15].

Although the slow-2 and slow-3 bands were typically discarded as physiological noises [14], they were still adopted in the correlation analysis for objective and comprehensive comparison in this study. In these two bands, a significant difference was found in several areas. However, further analysis failed to show significant correlation between Sunnybrook scores and ALFF values in facial synkinesis patients in the most significantly different cluster between the two groups (the right insula in the slow-2 band and the left thalamus in the slow-3 band).

Of note, the slow-4 and slow-5 bands were thought to be linked with neurophysiological processes, which were typically utilized in resting-state fMRI studies (below 0.1 Hz) [20, 21]. In the results of the slow-4 and slow-5 bands, we observed decreased ALFF values for neuronal activity in facial synkinesis patients in the right superior frontal cortex and right hippocampus and increased ALFF values predominantly in areas acting sensorimotor integration functions. Similar with the pattern of ALFF alternations in these two bands, the data analysis in the slow-6 band showed that facial synkinesis patients exhibited significantly increased ALFF values in areas of sensorimotor integration and bilateral temporal lobe, whereas it was decreased in the left right hippocampus and left cerebellum. Based on the results of post hoc two-sample *t*-test, ALFF values of the left insula showed the most significant difference between the two groups in these three frequency bands. And the ALFF value in the slow-6 band was most significantly correlated with Sunnybrook scores. Previous studies demonstrated that the slow-6 band was ascribed to low-frequency drifts [14, 19]. Although a few studies have addressed the indicative utilization of fluctuations in the slow-6 band, our data demonstrated its potential role of neurophysiological biomarker in the functional assessment of facial synkinesis patients.

**4.3. Insula and Motor Control.** This study demonstrated that facial synkinesis was mostly affected in areas of higher order processing sensorimotor information, including the postcentral cortex, insula, thalamus, ACC, hippocampus, and cerebellum. However, the patterns of ALFF alteration in the ACC or cerebellum areas were not fixed. It suggested that these changes were very likely to be caused by the motor-sensory mismatch due to the substantial prediction error. Among those heterogeneous results, it was interesting to find significant difference of ALFF in the insula between the two groups in each frequency band. Moreover, the ALFF values of the left insula in facial synkinesis patients in the slow-6 band were found to correlate with the improvement of facial nerve function significantly. The insula was demonstrated to contribute to hand and eye motor movement in motor control [22, 23]. The result indicated the motor control deficits in facial synkinesis. Recent neuroimaging studies have showed that the insula was associated with higher cognitive processing [24], pain, and sensorimotor processing [25, 26]. The insula participates in higher order processing of somatosensory input and has the most connections with other regions in the brain network, including the thalamus, hippocampus, and ACC [27–29]. In addition to pain, electrical stimulation of the human insula cortex elicits auditory, vestibular, vegetative, olfactory, and gustatory responses, thereby implying a multimodal role for the insula [30]. In the present study, the increased ALFF value in the insula ipsilateral to the lesioned side is considered to be in an abnormal state of hypercompensation in motor control of facial synkinesis patients.

**4.4. Possible Source of Artifacts.** Many studies paid attention to physiological signals arising from cardiac- and respiratory-related processes, for example, heart rate, respiration sources,

and blood pressure, which could impact regional measures of ALFF [31–34]. These physiological factors that are closely related with the quality of BOLD signals raise great concerns regarding test-retest reliability [35]. However, Zuo et al. have confirmed test-retest reliability of ALFF [14]. Baria et al. also demonstrated that it showed little difference from uncorrected ones when regressing out cardiac and respiration signal in each subject per voxel [36]. Besides, the noise was generally assumed a random factor in both groups. Thus, there should not be significant differences between the two groups, even when comparing the noise effect among the five frequency bands.

**4.5. Limitations.** This study was an explorative neuroimaging study, and several limitations should be noted. Firstly, the sample size was relatively small, which might have limited the power of persuasion. Secondly, it might be better to compare patients who have recovered from facial paralysis and those who suffered from facial synkinesis to investigate alterations of spontaneous activity caused by facial synkinesis only, although the functional activities in the related brain regions gradually recovered to the normal level with the gradual recovery of facial nerve function [37–39]. Considering unavailability of people recovered from facial paralysis, we recruited healthy normal control instead. Thirdly, the gender and age in the healthy controls did not match the patients perfectly. Finally, the variety of the disease duration was not well controlled, which could bring negative impact on homogeneity within the patient group.

## 5. Conclusion

We reported multiple changes of band-specific ALFF in facial synkinesis patients. The increased ALFF value in the slow-6 band in the ipsilateral insula was positively related with facial nerve function (Sunnybrook scores). This study revealed frequency-specific changes in local spontaneous neuronal activity for severity correlation in facial synkinesis, which could be a potential indicator of disease progression. It also provided valuable spatial information about the functionally aberrant regions, which implied the possible involvement of motor control system in facial synkinesis. Although it is with limitation, this study may broaden our vision of the neural mechanism of facial synkinesis.

## Data Availability

The data that support the findings of this study are available from the corresponding author, Jian-guang Xu, upon reasonable request.

## Conflicts of Interest

We have no financial or personal conflicts of interest to disclose.

## Acknowledgments

This study was financially supported by the Shanghai Jiaotong University Multidisciplinary Research Fund of Medicine and Engineering (YG 2016QN13).

## References

- [1] R. S. Baker, M. W. Stava, K. R. Nelson, P. J. May, M. D. Huffman, and J. D. Porter, "Aberrant reinnervation of facial musculature in a subhuman primate: a correlative analysis of eyelid kinematics, muscle synkinesis, and motoneuron localization," *Neurology*, vol. 44, no. 11, pp. 2165–2173, 1994.
- [2] C. J. Moran and J. G. Neely, "Patterns of facial nerve synkinesis," *Laryngoscope*, vol. 106, no. 12, pp. 1491–1496, 2010.
- [3] J. Husseman and R. P. Mehta, "Management of synkinesis," *Facial Plastic Surgery*, vol. 24, no. 2, pp. 242–249, 2008.
- [4] A. A. Pourmomeny and S. Asadi, "Management of synkinesis and asymmetry in facial nerve palsy: a review article," *Iranian Journal of Otorhinolaryngology*, vol. 26, p. 251, 2014.
- [5] L. Montserrat and M. Benito, "Facial synkinesis and aberrant regeneration of facial nerve," *Advances in Neurology*, vol. 49, pp. 211–224, 1988.
- [6] D. Choi and G. Raisman, "Somatotopic organization of the facial nucleus is disrupted after lesioning and regeneration of the facial nerve: the histological representation of synkinesis," *Neurosurgery*, vol. 50, no. 2, pp. 355–363, 2002.
- [7] K. D. Davis, K. S. Taylor, and D. J. Anastakis, "Nerve injury triggers changes in the brain," *The Neuroscientist*, vol. 17, no. 4, pp. 407–422, 2011.
- [8] Y. Wang, L. Yang, W. Wang, W. Ding, and H. Liu, "Decreased distance between representation sites of distinct facial movements in facial synkinesis—a task fMRI study," *Neuroscience*, vol. 397, pp. 12–17, 2019.
- [9] Y. Wang, W. W. Wang, X. Y. Hua, H. Q. Liu, and W. Ding, "Patterns of cortical reorganization in facial synkinesis: a task functional magnetic resonance imaging study," *Neural Regeneration Research*, vol. 13, no. 9, pp. 1637–1642, 2018.
- [10] C. M. Klingner, G. F. Volk, S. Brodoehl, O. W. Witte, and O. Guntinas-Lichius, "The effects of deafferentation without deafferentation on functional connectivity in patients with facial palsy," *NeuroImage: Clinical*, vol. 6, pp. 26–31, 2014.
- [11] X. N. Zuo and X. X. Xing, "Test-retest reliabilities of resting-state fMRI measurements in human brain functional connectomics: a systems neuroscience perspective," *Neuroscience and Biobehavioral Reviews*, vol. 45, pp. 100–118, 2014.
- [12] A. K. Engel, P. Fries, and W. Singer, "Dynamic predictions: oscillations and synchrony in top-down processing," *Nature Reviews Neuroscience*, vol. 2, no. 10, pp. 704–716, 2001.
- [13] M. Penttonen and G. Buzsáki, "Natural logarithmic relationship between brain oscillators," *Thalamus & Related Systems*, vol. 2, no. 2, pp. 145–152, 2003.
- [14] X. N. Zuo, A. di Martino, C. Kelly et al., "The oscillating brain: complex and reliable," *NeuroImage*, vol. 49, no. 2, pp. 1432–1445, 2010.
- [15] G. Buzsáki and A. Draguhn, "Neuronal oscillations in cortical networks," *Science*, vol. 304, no. 5679, pp. 1926–1929, 2004.
- [16] G. H. Chee and J. M. Nedzelski, "Facial nerve grading systems," *Facial Plastic Surgery*, vol. 16, no. 04, pp. 315–324, 2000.
- [17] Z. Yu-Feng, H. Yong, Z. Chao-Zhe et al., "Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI," *Brain & Development*, vol. 29, no. 2, pp. 83–91, 2007.
- [18] H. Yang, X. Y. Long, Y. Yang et al., "Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI," *NeuroImage*, vol. 36, no. 1, pp. 144–152, 2007.
- [19] B. Biswal, F. Z. Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI," *Magnetic Resonance in Medicine*, vol. 34, no. 4, pp. 537–541, 2010.
- [20] C. Demanuele, C. J. James, and E. J. Sonuga-Barke, "Distinguishing low frequency oscillations within the 1/f spectral behaviour of electromagnetic brain signals," *Behavioral and Brain Functions*, vol. 3, no. 1, p. 62, 2007.
- [21] M. D. Fox and M. E. Raichle, "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging," *Nature Reviews Neuroscience*, vol. 8, no. 9, pp. 700–711, 2007.
- [22] T. J. Anderson, I. H. Jenkins, D. J. Brooks, M. B. Hawken, R. S. J. Frackowiak, and C. Kennard, "Cortical control of saccades and fixation in man a PET study," *Brain*, vol. 117, no. 5, pp. 1073–1084, 1994.
- [23] G. R. Fink, R. S. J. Frackowiak, U. Pietrzyk, and R. E. Passingham, "Multiple nonprimary motor areas in the human cortex," *Journal of Neurophysiology*, vol. 77, no. 4, pp. 2164–2174, 1997.
- [24] M. A. Eckert, V. Menon, A. Walczak et al., "At the heart of the ventral attention system: the right anterior insula," *Human Brain Mapping*, vol. 30, no. 8, pp. 2530–2541, 2010.
- [25] F. Kurth, S. B. Eickhoff, A. Schleicher, L. Hoemke, K. Zilles, and K. Amunts, "Cytoarchitecture and probabilistic maps of the human posterior insular cortex," *Cerebral Cortex*, vol. 20, no. 6, pp. 1448–1461, 2010.
- [26] L. J. Chang, T. Yarkoni, M. W. Khaw, and A. G. Sanfey, "Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference," *Cerebral Cortex*, vol. 23, no. 3, pp. 739–749, 2013.
- [27] C. Simões and R. Hari, "Relationship between responses to contra- and ipsilateral stimuli in the human second somatosensory cortex SII," *NeuroImage*, vol. 10, no. 4, pp. 408–416, 1999.
- [28] A. Caria, R. Veit, R. Sitaram et al., "Regulation of anterior insular cortex activity using real-time fMRI," *NeuroImage*, vol. 35, no. 3, pp. 1238–1246, 2007.
- [29] I. Mutschler, B. Wieckhorst, S. Kowalevski et al., "Functional organization of the human anterior insular cortex," *Neuroscience Letters*, vol. 457, no. 2, pp. 66–70, 2009.
- [30] L. Mazzola, J. Isnard, and F. Mauguière, "Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses," *Cerebral Cortex*, vol. 16, no. 7, pp. 960–968, 2006.
- [31] R. G. Wise, K. Ide, M. J. Poulin, and I. Tracey, "Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal," *NeuroImage*, vol. 21, no. 4, pp. 1652–1664, 2004.
- [32] R. M. Birn, J. B. Diamond, M. A. Smith, and P. A. Bandettini, "Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI," *NeuroImage*, vol. 31, no. 4, pp. 1536–1548, 2006.
- [33] M. Bianciardi, M. Fukunaga, P. van Gelderen et al., "Sources of functional magnetic resonance imaging signal fluctuations in the human brain at rest: a 7 T study," *Magnetic Resonance Imaging*, vol. 27, no. 8, pp. 1019–1029, 2009.
- [34] L. Yan, Y. Zhuo, Y. Ye et al., "Physiological origin of low-frequency drift in blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI)," *Magnetic Resonance in Medicine*, vol. 61, no. 4, pp. 819–827, 2010.



- [35] R. Marchitelli, L. Minati, M. Marizzoni et al., “Test-retest reliability of the default mode network in a multi-centric fMRI study of healthy elderly: effects of data-driven physiological noise correction techniques,” *Human Brain Mapping*, vol. 37, no. 6, pp. 2114–2132, 2016.
- [36] A. T. Baria, M. N. Baliki, T. Parrish, and A. V. Apkarian, “Anatomical and functional assemblies of brain BOLD oscillations,” *Journal of Neuroscience*, vol. 31, no. 21, pp. 7910–7919, 2011.
- [37] T. Bitter, B. Sorger, V. Hesselmann, B. Krug, K. Lackner, and O. Guntinas-Lichius, “Cortical representation sites of mimic movements after facial nerve reconstruction: a functional magnetic resonance imaging study,” *Laryngoscope*, vol. 121, no. 4, pp. 699–706, 2011.
- [38] H. Wu, H. Kan, C. Li et al., “Effect of acupuncture on functional connectivity of anterior cingulate cortex for Bell’s palsy patients with different clinical duration,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 646872, 7 pages, 2015.
- [39] M. Rijntjes, M. Tegenthoff, J. Liepert et al., “Cortical reorganization in patients with facial palsy,” *Annals of Neurology*, vol. 41, no. 5, pp. 621–630, 2010.