Patterns of cortical reorganization in facial synkinesis: a task functional magnetic resonance imaging study

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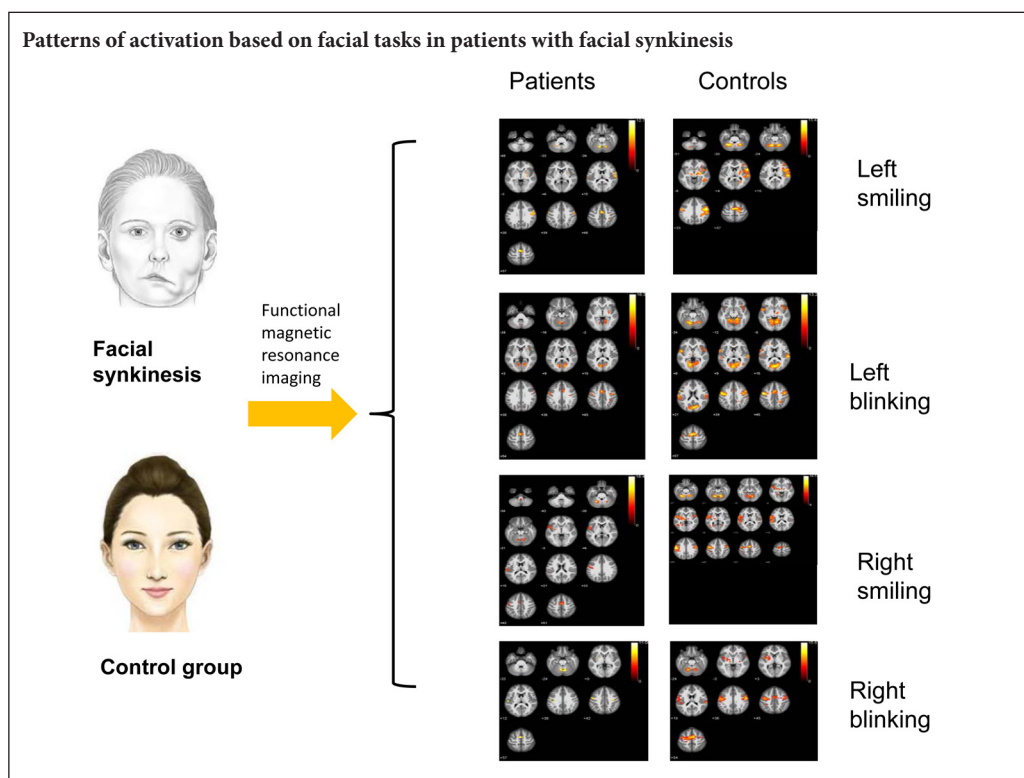2 Department of Radiology, Huashan Hospital, Fudan University, Shanghai, China
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Graphical Abstract

Patterns of activation based on facial tasks in patients with facial synkinesis

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Abstract

Facial synkinesis, a sequela of peripheral facial nerve palsy, is characterized by simultaneous involuntary facial movement during a voluntary desired one. Maladaptive cortical plasticity might be involved in the dysfunction of facial muscles. This cohort study investigated the cortical functional alterations in patients with facial synkinesis, using the task functional magnetic resonance imaging. Facial motor tasks, including blinking and smiling, were performed by 16 patients (aged 30.6 ± 4.5 years, 14 females/2 males) and 24 age- and sex-matched healthy controls (aged 29.1 ± 4.2 years, 19 females/5 males). Results demonstrated that activation in the cortico-facial motor representation area was lower during tasks in patients with facial synkinesis compared with healthy controls. Facial movements on either side performed by patients caused more intensive activation of the supplementary motor area on the contralateral side of the affected face, than those on the unaffected side. Our results revealed that there was cortical reorganization in the primary sensorimotor area and the supplementary motor area. This study was registered in Chinese Clinical Trial Registry (registration number: ChiCTR1800014630).

Key Words: nerve regeneration; facial synkinesis; functional magnetic resonance imaging; neural plasticity; cortical representation; block design; facial movement; blinking; smiling; neural regeneration

Introduction

A sequelae of severe peripheral facial nerve palsy is facial synkinesis, characterized by simultaneous involuntary facial movement during a voluntary desired one (Moran and Neely, 1996). The common synkinetic patterns, oral-ocular synkinesis and ocular-oral synkinesis, mainly involve the orbicularis oris muscles and the orbicularis oculi muscle, which are innervated by different branches of the facial nerve (Nakamura et al., 2003). The underlying pathological mechanism of facial synkinesis remains unanswered. Some researchers believe that the facial synkinesis following peripheral facial palsy is mainly due to the misguidance of regenerated axons, which have innervated the incorrect muscles (Montserrat and Benito, 1988). Paradoxically, the interval between facial nerve injury and the emergence of synkinesis in some cases is shorter than the theoretical period for any misdirected regeneration (May, 1983). Various animal studies demonstrated that the functional reorganization in the cortex following facial nerve injury could occur within hours after the onset of the lesion (Huntley, 1997). In addition, some investigators have shown changes of cortico-facial motor representations following facial nerve injury (Bitter et al., 2011; Klingner et al., 2011). Therefore, we considered that the central nervous system might be involved in dysfunction of facial muscles. Despite the well-established representation in the motor cortex for facial movements, we know of few studies that have investigated cortical functional alterations in patients with facial synkinesis. The current study aims to map the sensorimotor representation area of synkinetic movements by using block-designed functional magnetic resonance imaging (fMRI) with multiple facial actions.

Subjects and Methods

Subjects

A total of 16 patients with unilateral synkinesis following peripheral facial nerve palsy were randomly enrolled in this cohort study from the Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University, China. The control group was composed of 24 age- and sex-matched healthy subjects recruited publicly. For the patient group, the inclusion criteria consisted of: (1) a history of oral-ocular synkinesis for a period greater than 9 months, (2) absence of nerve transposition, and (3) the ability to follow instructions. Exclusion criteria for both groups were as follows: (1) confirmed or suspected history of cardiopulmonary failure, (2) psychiatric disorders; (3) concurrent peripheral neuropathy, and (4) contraindications to investigation by MRI. There were no significant differences in age or sex between the two groups. All patients showed a unilateral facial synkinesis (**Table 1**). The following fMRI study was approved by the Ethics Committee of the Shanghai Jiao Tong University (approval No. 2017-365-T267). Written informed consent was obtained from all volunteers and patients prior to the study. This study was registered in Chinese Clinical Trial Registry (registration number: ChiCTR1800014630). The flow chart for the procedures was shown in **Figure 1**.

Design and motor tasks

In the motor scans, participants were asked to execute four motor tasks: (1) Left eye blinking, (2) right eye blinking, (3) smiling on the left side, (4) smiling on the right side. The unilateral eye blinking was characterized by the rhythmic blinking of one eye, and smiling on the either side of the mouth was defined as unilateral contraction of the muscles innervated by a buccal branch. Patients were photographed for the above-mentioned tasks. During the scan, all subjects were instructed to perform repetitive movements rhythmically in response to visual signals. These were projected by a video projector onto a screen and reflected on a mirror attached to the head coil. Each action lasted for 30 seconds, alternating with another 30-second rest period. This was conducted three times. There were six blocks of fMRI scan for each task. The activation was calculated by comparison of the three scans of task and the three scans of rest. Before the beginning of the experiment, all subjects were trained on the tasks for approximately 20 minutes. The facial movements of each subject were recorded by camera.

Data acquisition

All imaging data were obtained with a 3.0 T GE Signa VH/I 3.0-T scanner (GE Healthcare, GE Asian Hub, Shanghai, China) equipped with a 32-channel head coil. The subject's head was held between a pair of cushions, one on each side of the head, to minimize head movements. fMRI data were measured with an echo-planar imaging sequence (repetition time/echo time = 3000/35 ms, field of view = 240 mm × 240 mm, 43 axial slices, acquisition matrix = 64 × 64, voxel size = 3.4 mm × 3.4 mm × 3.2 mm, flip angle = 90°). Structural imaging data were acquired with a multiecho MPRAGE T1-weighted pulse sequence (repetition time/echo time = 1000/5 ms, TI = 1200 ms, flip angle = 200°, field of view = 240 mm × 240 mm, acquisition matrix = 256 × 256, sagittal acquisition, spatial resolution = $1 \times 1 \times 1$ mm^3, interslice space = 0 mm).

Data analysis

The image data were analyzed with the Statistical Parametric Mapping Program (SPM 8, Wellcome Institute for Imaging Neuroscience, London, UK) implemented in MATLAB (MathWorks, Natick, MA, USA). The EPI of each individual was realigned to the first image for each sequence separately for interscan movement artifacts. Their aligned functional images from all sessions were normalized by DARTEL to the Montreal Neurological Institute (MNI) standard brain for reporting MNI coordinates. Finally, the images were spatially smoothed using a 6-mm full width at half maximum Gaussian kernel. We made boxcar analysis with T-contrast for all sessions of every subject and retained only voxels with Z scores > 4.3946 for a *P*-value of 0.05 at voxel level with family-wise error correction for single-subject analysis. The group analysis for each session was performed using a one sample *t*-test. Voxels only with T scores > 2.8965 for a *P*-value of 0.05 at voxel level with false discovery rate correction were retained (Genovese et al., 2002). Before the analysis,

Table 1 Demographic information of facial synkinesis patients and healthy controls

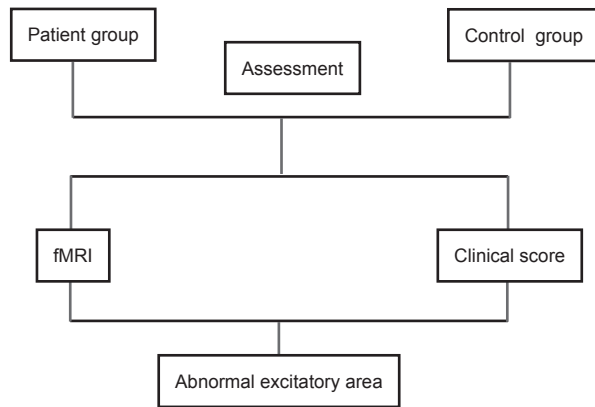| Item	Patient group (*n* = 16)	Control group (*n* = 24)	*P* value
Age (mean±SD, year)	30.6±4.5	29.1±4.2	0.306[a]
Sex (female/male, *n*)	14/2	19/5	0.681[b]

[a]Two independent sample *t*-test; [b]Chi-square test.

Figure 1 Flowchart of functional magnetic resonance imaging (fMRI) study in facial synkinesis patients and healthy controls.

the activation maps obtained during the movement task of the left side were flipped along the y-axis for assessing differences in the activation patterns between the motor tasks of the affected and unaffected side.

Results

Activation of brain regions during the smiling task in the healthy subjects and facial synkinesis patients

The control group showed significant activation of the contralateral primary sensorimotor cortex and minor activation of the ipsilateral primary sensorimotor cortex during the smiling task on either side. Activation also existed in the bilateral supplementary motor area (**Figure 2A** and **Table 2**).

For the patient group, the smiling task on the affected side mainly activated the contralateral primary sensorimotor cortex and supplementary motor area (**Figure 2B** and **Table 2**). Compared with the former, the smiling task on the unaffected side (left side) caused more significant activation, especially in the primary sensorimotor cortex of the contralateral side (**Figure 2C** and **Table 2**).

Activation of brain regions during the blinking task in the healthy subjects and facial synkinesis patients

During the blinking task movement, the primary sensorimotor cortex and the supplementary motor area were bilaterally activated (**Figure 2D** and **Table 3**).

When performing the blinking task on the affected side (right side), patients showed activation of the contralateral primary sensorimotor cortex (**Figure 2E** and **Table 3**). Conversely, activation was found bilaterally in the primary sensorimotor cortices during the blinking task on the unaf-

Table 2 Brain regions activated by right-mouth movement in healthy subjects and right- or left-mouth movement in patients with facial synkinesis

Region label	MNI coordinates			Voxels	Peak intensity	*P*
	x	y	z			
Healthy subjects						
Postcentral_L	−51	−15	33	1672	14.73	0.001
Insula_L	−42	0	−3	1672	9.576	0.001
Temporal_Sup_L	−54	−33	18	1672	9.129	0.001
Cerebellum_6_L	−27	−63	−27	842	14.699	0.001
Cerebellum_6_R	18	−63	−21	842	13.238	0.001
Cerebellum_6_L	−6	−69	−15	842	7.862	0.001
Supp_Motor_Area_L	−3	−3	51	408	12.844	0.001
Paracentral_Lobule_L	−18	−15	66	408	6.859	0.001
Postcentral_R	57	0	33	214	9.873	0.001
Thalamus_L	−12	−15	0	154	9.454	0.001
Facial synkinesis patients						
Right-mouth movement						
Cerebellum_6_L	−24	−63	−30	109	18.429	0.001
Rolandic_Oper_L	−48	3	0	107	15.721	0.001
Supp_Motor_Area_L	0	−6	51	163	11.444	0.001
SupraMarginal_L	−60	−24	15	41	10.911	0.001
Cerebellum_6_R	9	−66	−21	79	10.286	0.001
Postcentral_L	−45	−12	33	74	9.388	0.001
Pallidum_L	−24	−6	−3	14	9.203	0.001
Left-mouth movement						
Supp_Motor_Area_L	−6	0	57	185	12.788	0.001
Cerebellum_6_L	−12	−63	−21	114	12.362	0.001
Cerebellum_6_L	−30	−57	−33	114	8.294	0.001
Precentral_R	63	6	15	278	11.482	0.001
Postcentral_R	51	−12	33	278	11.247	0.001
Cerebellum_6_R	15	−66	−24	46	9.821	0.001
Precentral_L	−57	0	39	14	9.612	0.001
Pallidum_R	24	0	0	20	9.083	0.001

A one-sample *t*-test was used to identify significant voxels. The *P* value was set to 0.001 and the corresponding *T* threshold was then determined by the *P* value. The peak intensity in each cluster was reported. R: Right; L: left; MNI: Montreal Neurological Institute.

fected (left) side (**Figure 2F** and **Table 3**).

It is noteworthy that, for patients, facial movements on either side caused more intensive activity in the supplementary motor area on the unaffected side, than those on the affected side. Nevertheless, the activation during movements on the unaffected side of the patient group was lower than those in the control group.

Discussion

Facial synkinesis is one of the most unpleasant sequelae of peripheral facial nerve palsy. The efficacy of traditional surgical therapy, including high selective muscle resection and selective neurolysis, has not been satisfactory due to the serious complications or high recurrence rate (Husseman and Mehta, 2008). Despite the effects of botulinum toxin treatment to relieve the symptoms (Laskawi, 2008), facial synkinesis is extremely difficult to deal. The lack of clarity of the pathophysiological mechanism has been the main obstacle in contributing to the poor clinical outcomes. It is gen-
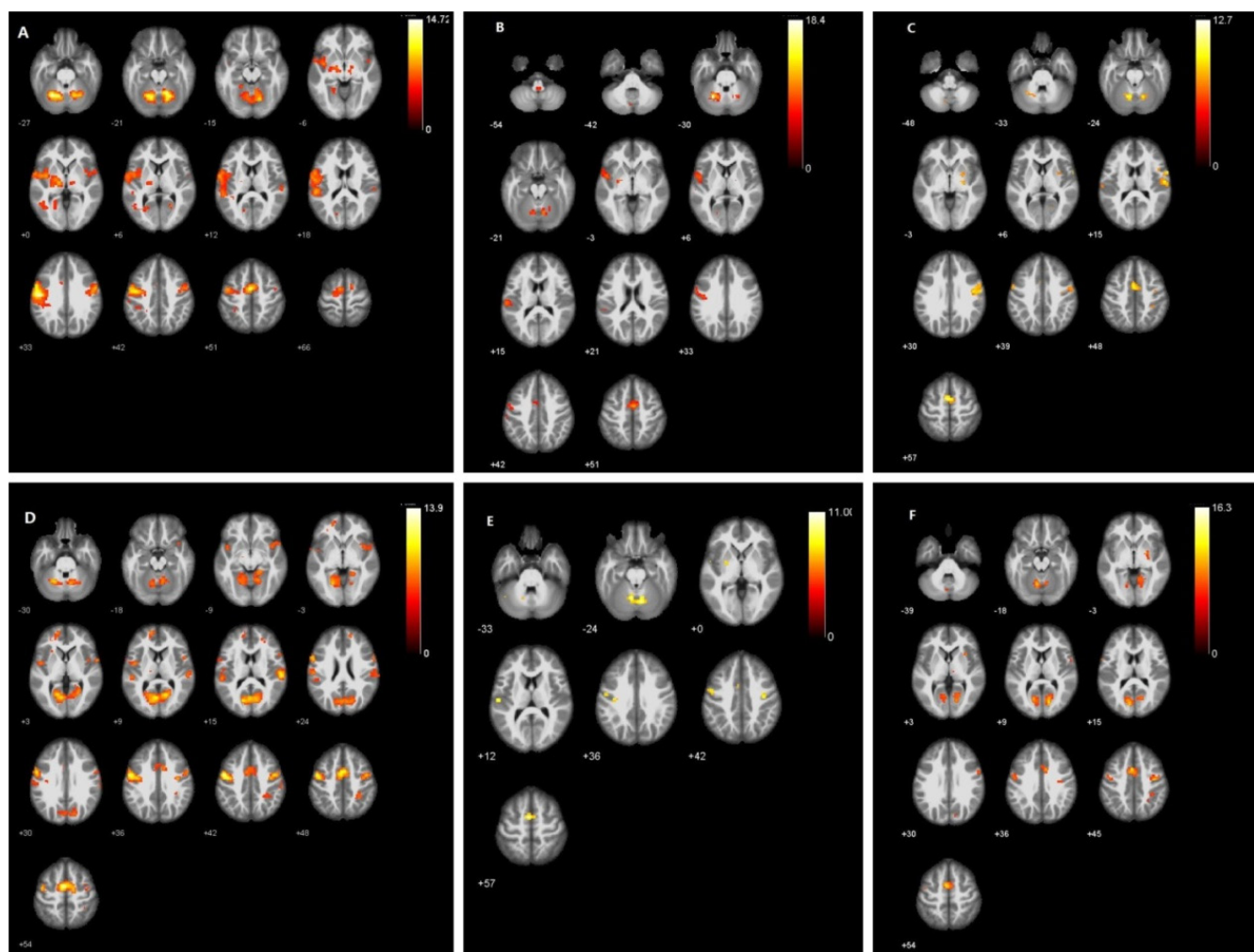
Figure 2 Activation maps of brain regions in healthy subjects and peripheral facial nerve palsy patients during facial movements.
(A) Activated brain regions in the control group during smiling. (B) Activated brain regions in the patient group on the affected side during smiling. (C) Activated brain regions in the patient group on the unaffected side during smiling. (D) Activated brain regions in the control group during blinking. (E) Activated brain regions in the patient group on the affected side during blinking. (F) Activated brain regions in the patient group on the unaffected side during blinking. The warm color bar is used to define the activation of the voxels. Red-yellow suggests a positive activation in the brain area. The numbers in the figures correspond to the slice numbers in the CH2 brain template. Control group: Healthy subjects; patient group: peripheral facial nerve palsy patients with unilateral synkinesis.

erally known that the injury and regeneration of peripheral nerve might result in plastic changes (Navarro et al., 2007), which can occur at multiple levels of the nervous system. Severe facial nerve damage results in synaptic reorganization in the facial nucleus, motoneuronal hyperexcitability and changes in the peripheral nerve activity (Oge et al., 2005). Investigations are necessary not only of the subcortical levels, including the peripheral nerves and brain stem, but also of the maladaptation of cortical reorganization. The present study provides an insight into the association between the clinical symptoms of facial synkinesis and the subserving activity pattern in the central nervous system. This is the first investigation that has attempted to map cortico-facial motor representations in facial synkinesis using fMRI.

Our results showed that in both the primary sensorimotor cortex and the premotor cortex, there are two distinct functional clusters devoted to the control of facial motor actions. This is basically consistent with a previous study (Morecraft

et al., 2004), which indicates that the cortical network subserving facial motor function mainly consists of the primary motor cortex, the ventral lateral premotor cortex and the supplementary motor cortex. We also noticed activation in postcentral gyrus, even though the somatosensory afferents of the face are mediated by the trigeminal nerve and facial muscles have some internal sensory receptors. Bitter et al. (2011) have suggested that changes in representation of the face should be present only in the motor cortex, but not in the somatosensory cortex. However, animal studies have found that corticospinal neurons are present in the primary sensory cortex, which was verified by retrograde trans-synaptic tracing labeling (Rathelot and Strick, 2006). Another explanation is that motor cortex activity can drive changes in the network state of the somatosensory cortex through a cortico-cortical feedback pathway (Zagha et al., 2013). Some of our findings might indicate the close connection between the motor and somatosensory cortices in active motor para-

Table 3 Brain regions activated by right-eyelid movement in controls and right- or left-eyelid movement in patients with facial synkinesis

Region label	MNI coordinates			Voxels	Peak intensity	P
	X	Y	Z			
Healthy subjects						
Supp_Motor_Area_L	−6	−3	57	641	13.903	0.001
Supp_Motor_Area_R	15	−12	54	641	9.196	0.001
Cingulate_Mid_R	12	9	36	641	7.916	0.001
Postcentral_L	−51	−6	42	606	12.684	0.001
Precentral_L	−60	6	24	606	9.577	0.001
Temporal_Sup_L	−54	−30	12	606	9.412	0.001
Temporal_Sup_R	60	−27	15	174	11.38	0.001
Calcarine_L	−15	−75	12	1443	10.99	0.001
Cerebellum_6_L	−24	−60	−30	1443	10.704	0.001
Calcarine_R	15	−66	9	1443	10.281	0.001
Precentral_R	48	−3	45	194	10.83	0.001
Precentral_R	60	6	24	194	7.84	0.001
Facial synkinesis patients						
Right-eyelid movement						
Supp_Motor_Area_L	−6	−3	57	92	11.005	0.001
Cerebellum_6_L	−9	−60	−24	108	9.841	0.001
Cerebellum_6_R	9	−69	−24	108	9.826	0.001
Location not in atlas	39	−12	42	20	8.763	0.001
Putamen_L	−24	−3	3	14	8.525	0.001
Postcentral_L	−51	−12	36	43	8.202	0.001
Left-eyelid movement						
Calcarine_R	15	−75	6	705	16.314	0.001
Calcarine_L	−15	−75	12	705	12.447	0.001
Cerebellum_6_L	−9	−66	−18	705	10.866	0.001
Supp_Motor_Area_L	−6	0	54	295	13.244	0.001
Cingulate_Mid_R	9	9	36	295	9.892	0.001
Precentral_R	39	−12	48	70	11.313	0.001
Precentral_L	−57	0	39	53	10.044	0.001
Pallidum_R	24	−3	−3	27	9.932	0.001

A one-sample *t*-test was used to identify significant voxels. The *P* value was set to 0.001 and the corresponding *T* threshold was then determined by the *P* value. The peak intensity in each cluster was reported. R: Right; L: left; MNI: Montreal Neurological Institute.

digms even when only one system is involved.

In the control group, all facial representations seem to be bilaterally activated with a contralateral prevalence during unilateral movements. The areas activated by smiling (unilateral contraction of the risorius and zygomaticus) are mainly restricted in the contralateral motor cortex with minimal involvement of ipsilateral motor cortex. However, the cortical motor representation of blinking (eyelid movements) is symmetrical, with a slight predominance of contralateral activation. These results by and large confirmed the traditional viewpoint that the innervation of the face is bilaterally controlled for the upper part and mainly contralaterally controlled for the lower part (Cattaneo and Pavesi, 2014; Morecraft et al., 2004). The patient group, however, showed no comparable activation in the ipsilateral primary motor cortex during eyelid movements on the affected side. When they performed the same task contralaterally, the activation patterns were similar to those of the controls, *i.e.*, there was bilateral activation of the primary motor cortex. One explanation could be that the ipsilateral cortical facial

areas are spared, preventing hemisphere injury from an adverse impact on upper facial motor function. For eyelid movement, damage to the motor output site is more likely to cause eyelid dyskinesia than injury to the contralateral cortex.

Facial movements on either side performed in the patient group caused more intensive activation of the supplementary motor area on the contralateral side of the affected face, than those on the unaffected side. Nevertheless, in the control group, the supplementary motor areas bilaterally were markedly activated with contralateral prevalence during either facial task. A previous study revealed that more supplementary motor area neurons contributed to contralateral movements than to ipsilateral movements (Tanji et al., 1988). Accordingly, it is supposed that unilateral facial synkinesis was responsible for the above activation patterns in the supplementary motor area. In the brain, the supplementary motor area is one of vital areas that contribute to motor planning and modulates complex movement impulses transferred from the primary motor cortex to the motor nuclei within the brainstem. It also coordinates voluntary movements as well as involuntary movements (Nachev et al., 2008). A recent fMRI study demonstrated that the supplementary motor area is involved in the linkage of movements in different limbs, suggesting that even involuntary coordination of movement invokes a distributed network coordinated by the supplementary motor area (Salardini et al., 2012). It has been argued that supplementary motor area activity is evoked by the urge to move rather than the movement per se (Fried et al., 1991). Additionally, the increased activity of the supplementary motor area could be associated with the suppression of involuntary movements during the execution of self-paced movements (Finis et al., 2013). This could explain how the control of inappropriate movements, through increased awareness of imminent facial expressions, leads to the increased activity of the supplementary motor area.

Compared with healthy controls, patients with facial synkinesis demonstrated weak motor cortex activation during all tasks. We postulated that the maladaptive process is due to the denervation of facial muscles and the taking over of the functions of neighboring cortical areas after facial nerve injury. As described in a previous study, using transcranial magnetic stimulation and positron emission tomography, a shift of neighboring cortical areas replaced the deafferented area in severe facial palsy (Rijntjes et al., 1997). Remarkably for our patients, their activated voxel number and the average signal intensity in movements on the unaffected side were lower than those in controls, despite being still higher than those in affected counterparts. We presume that distinguishing of activation in different cerebral hemispheres was associated with the frequency of using facial muscles. Patients usually avoided the use of facial expressions, even on their unaffected side, to maintain the symmetry of facial movements.

The limitations of this study are as follows: The sample size is relatively small, and there is no detailed classifica-

tion of the patient group. It lacks a comparison to a control group with unilateral complete facial paralysis.

In conclusion, our fMRI study reveals the patterns of activation based on facial tasks in patients with facial synkinesis. The recognition of multiple cortico-facial motor representations provides the opportunity to study the functional role of cortex neuroplasticity in facial synkinesis and how it impacts the control of facial movements. Physiotherapy modalities, including electromyogram biofeedback through neuromuscular re-education, have been found to be effective for facial synkinesis (Pourmomeny et al., 2014). This study explores cortical functional reorganization linked to facial synkinesis, and provides a theoretical basis for optimizing innovative medical therapies.

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