

Time-course of Changes in Activation Among Facial Nerve Injury

A Functional Imaging Study

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Abstract: Patients suffering different intervals of facial nerve injury were investigated by functional magnetic resonance imaging to study changes in activation within cortex.

Forty-five patients were divided into 3 groups based on intervals of facial nerve injury. Another 16 age and sex-matched healthy participants were included as a control group. Patients and healthy participants underwent task functional magnetic resonance imaging (eye blinking and lip pursing) examination.

Functional reorganization after facial nerve injury is dynamic and time-dependent. Correlation between activation in sensorimotor area and intervals of facial nerve injury was significant, with a Pearson correlation coefficient of -0.951 ($P < 0.001$) in the left sensorimotor area and a Pearson correlation coefficient of 0.333 ($P = 0.025$) in the right sensorimotor area.

Increased activation in integration areas, such as supramarginal gyrus and precunes lobe, could be detected in the early-middle stage of facial dysfunction compared with normal individuals. Decreased activation in sensorimotor area contralateral to facial nerve injury could be found in late stage of facial dysfunction compared with normal individuals. Dysfunction in the facial nerve has devastating effects on the activity of sensorimotor areas, whereas enhanced intensity in the sensorimotor area ipsilateral to the facial nerve injury in middle stage of facial dysfunction suggests the possible involvement of interhemispheric reorganization. Behavioral or brain stimulation technique treatment in this stage could be applied to alter reorganization within

sensorimotor area in the rehabilitation of facial function, monitoring of therapeutic efficacy, and improvement in therapeutic intervention along the course of recovery.

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Abbreviations: fMRI = functional magnetic resonance imaging, HBS = House-Brackmann score, MRI = magnetic resonance imaging.

INTRODUCTION

Brain reorganization can lead to a certain degree of functional adaptation after nerve injury.^{1,2} During functional reorganization, changes are often not precisely fixed to 1 brain area, because pathological disorders in brain often include damages to various regions, combining with an altering of the neuroanatomical pathways.^{3,4} Reorganization within cerebral cortex contains 3 routes: intrahemispheric reorganization, interhemispheric reorganization, and recruitment of new areas in either hemisphere.⁵ The mechanism was considered as an important factor in evaluating functional rehabilitation.⁶

Facial nerve injury (FNI) is a common complication from acoustic neuroma surgery, and in some cases, it is an irreversible condition. In previous studies, it has been found that lesions in peripheral motor nerves could lead to central cortical reorganization.⁷⁻¹⁰ The area mostly associated with facial movement is located in the primary sensorimotor area.^{11,12} Previous studies have emphasized this area has dynamic and adaptive mechanisms that mediate motor and cognitive integration in learning and memory.^{13,14} These findings raise the possibility that these cortical changes may be crucial in determining how well a patient adapts to circumstance alterations.¹⁵

Interestingly, the facial nucleus contains 2 different types of motor neurons. One type, which innervates the perioral muscles, receives a purely contralateral input from the primary sensorimotor cortex. By contrast, the other type, which innervates the periorbital muscles, receives a bilateral input from the primary sensorimotor cortex.¹⁶ This difference in anatomy may result in differences in cortical reorganization.

The aim of this study was to examine the brain reorganization in patients with facial nerve injury after acoustic neuroma surgery as compared with healthy individuals. The correlation between activation intensity in the sensorimotor area and the time intervals of suffering facial nerve injury was also calculated. It is encouraging to note that a better understanding of brain reorganization after facial nerve injury could provide effective measurements for facial function rehabilitation, monitoring of therapeutic efficacy, and improvement in therapeutic intervention along the course of recovery.¹⁷

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METHODS

Participants

Patients were recruited from the Department of Neurosurgery, Beijing Tian Tan Hospital, Capital Medical University. All patients had facial nerve injury from acoustic neuroma surgery. Patients with other neoplastic conditions in the cerebellar-pontine angle (CPA) or other neurological disorders were excluded from the study. The participants of the patient group had to fulfill 4 further criteria to eliminate other possible interferences: to have been diagnosed with acoustic neuroma by magnetic resonance imaging (MRI) combined with pathology; to have presented with facial dysfunction after acoustic neuroma surgery; to have facial nerve anatomically preserved during acoustic neuroma surgery; and to have not required any medical therapy during facial dysfunction.

The Investigational Review Board (IRB) of Beijing Tian Tan Hospital, Capital Medical University, approved the study. Forty-five participants who gave informed written consent before their participation were divided into 3 groups, which was based on the intervals of their facial nerve injury. The first group, called facial nerve injury (FNI)1 group, suffered from facial nerve injury of less than 6 months ($n = 15$, 7 female patients, with a mean age of 33.57 ± 9.14 y); the second group, called FNI2 group, suffered from facial nerve injury of more than 6 months and less than 1 year ($n = 15$, 8 female patients, with a mean age of 37.43 ± 9.24 y); and the third group, called FNI3 group, suffered from facial nerve injury of more than 1 year and less than 2 years ($n = 15$, 6 female patients, with a mean age of 35.86 ± 9.91 y).

All patients were right-handed and had facial nerve injury in the right side. The House-Brackmann score (HBS), in which a score of 1 represents a healthy facial movement and a score of 6 represents no facial movement, is the most widely used facial nerve grading system in the clinical assessment of facial function.¹⁸ All patients had complete facial dysfunction with HBS in the range of 5 to 6. Another 16 right-handed, age and sex-matched healthy participants (8 female participants, with a mean age of 36.2 ± 8.83 y) were recruited as a control group.

Acquisition of Magnetic Resonance Imaging Data

The functional MRI data were acquired on a Magnetom Trio 3T (Siemens AG, Erlangen, Germany) MRI scanner. Echo planar imaging-based functional MR images were collected with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90° , field of view (FOV) = 224×224 , matrix = 64×64 , number of slices = 33, slice thickness = 3 mm, and a gap = 0.75 mm. For anatomical reference, a whole brain 3D MPRAGE dataset (with the following scan parameters: TR = 2300 ms, TE = 3.01 ms, FA = 9° , FOV = 240×240 , number of slices = 176, slice thickness = 1 mm isotropic) was scanned for every participant immediately after functional MRI (fMRI) examination.

There were 2 tasks in the facial movement assessment: eye blinking (lifting the eyebrows, closing eyes gently); and lip pursing. Participants were asked to remain relaxed or execute certain tasks by following the instructions that were presented to them by the projector. In each task, after an 8-second rest period, 6 blocks with a 40-second duration were run continuously in which each block consisted of 20-second self-pace movements with a frequency of 1 Hz, which was followed by a 20-second period of rest. During the rest block, the participants were instructed to relax. All participants were instructed to keep

their head stable during the movements. The eye blinking task consisted of fast, gentle, self-paced bilateral closure of the eyelids, in which the participants were instructed not to use other facial muscles during the task. The lip-pursing task was a self-paced repetitive kiss-like movement with the lips.

Functional Magnetic Resonance Imaging Data Analyses

Datasets were preprocessed and analyzed using Statistical Parametric Mapping-8 software (<http://www.lion.ucl.ac.uk/spm/software/spm8>). The preprocessing pipelines included the following: slice timing, spatial realignment to correct for subject motion, spatial normalization to the Montreal Neurological Institute (MNI) template space, and spatial smoothing using a 8-mm full-width, at half-maximum Gaussian smoothing kernel.

Activation maps of eye-blinking and lip-pursing tasks were calculated, respectively. One-sample *t* test was used to investigate the activation maps in eye-blinking task and lip-pursing task among healthy control group. Two-sample *t* tests were used to test for areas of increased or decreased activation in the 3 facial nerve injury groups relative to the normal healthy group. And the results were reported using the software of xjView in SPM8 (<http://www.alivelearn.net/xjview/ad.php>) at a threshold false discovery rate (FDR) corrected value of $P = 0.01$, 10 voxels minimum.^{19,20}

Correlation analysis between the activation intensity in sensorimotor area of the lip-pursing task results and the intervals of facial nerve injury was calculated. Determination of sensorimotor areas has been demonstrated in the study by Jurkiewicz et al,¹⁷ which was posterior bank of the precentral gyrus and anterior bank of the postcentral gyrus, including the central sulcus and the paracentral lobule. The activation intensity in sensorimotor area was represented by Z value in SPM8, for family-wise error (FWE) corrected value of $P = 0.05$, 10 voxel minimum.^{21,22} In addition, curve fitting between the Z value in sensorimotor area in the lip-pursing task results and the intervals of facial nerve injury was also shown, with a threshold alpha value of $P < 0.05$ (SPSS v.17.0 statistical software program).

In the fMRI study, it was challenging to obtain satisfactory functional MR data because the head motion during movements creates artifacts on the images. To avoid artifacts that were provoked by head motion, the study discarded data from participants whose head motions were evaluated on moving more than 0.3 mm with SPM8 software processing. Interference from head motion artifacts were compared between groups by 2-sample *t* test, with a statistical threshold of $P < 0.05$ (SPSS v.17.0).

RESULTS

Functional Magnetic Resonance Imaging

Comparison of head motion artifact between groups is shown in Table 1, which shows there was no significant head-motion difference between groups.

Activation within the cerebral cortex in the eye-blinking task and the lip-pursing task among the healthy control group was shown in Figure 1. For the FNI1 group, increased activation in bilateral postcentral gyrus and bilateral inferior parietal lobe was detected in the eye-blinking task results as compared with the healthy control group (Fig. 2A and B), and increased activation in bilateral precuneus lobe was observed in the lip-pursing task results as compared with the healthy control group (Fig. 2C and D). For the FNI2 group, increased activation in the right supramarginal gyrus was detected in both the

TABLE 1. Comparison of Head Motion Artifact Between Groups

Group/Task	Eye Blinking	Lip Pursing
Normal healthy individuals	0.004844 ± 0.004534 mm	0.004159 ± 0.002522 mm
Facial nerve injury lasting less than 6 mos	0.006028 ± 0.002675 mm	0.006044 ± 0.002625 mm
Facial nerve injury lasting 6 mos to 1 y	0.003892 ± 0.001853 mm	0.004808 ± 0.004063 mm
Facial nerve injury lasting 1–2 y	0.005527 ± 0.004756 mm	0.005322 ± 0.002813 mm

P > 0.05, with no significantly statistical differences.

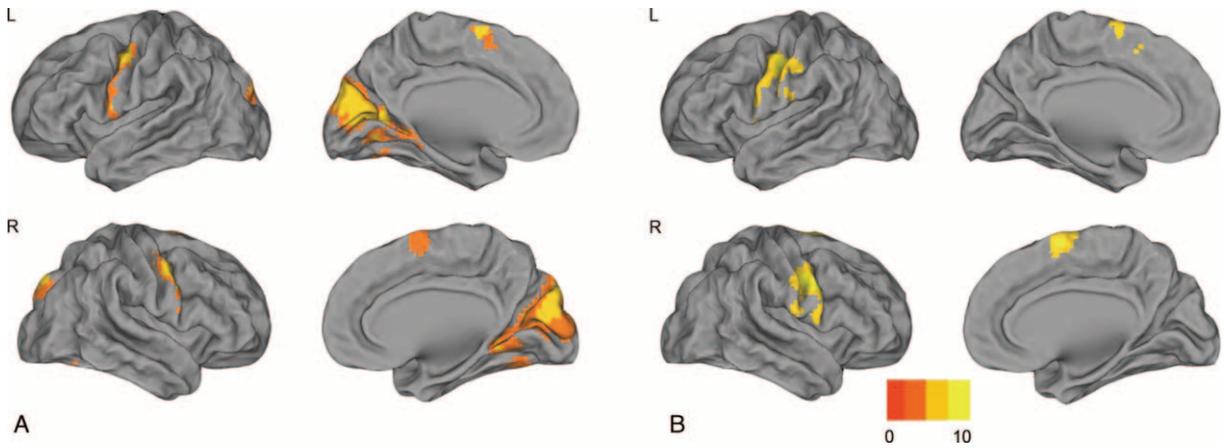


FIGURE 1. Activation within cerebral cortex in eye blinking task and lip pursing task among healthy control group. Activation of bilateral sensorimotor area, bilateral supplementary motor area, bilateral precuneus lobe, bilateral cuneus lobe, and bilateral calcarine sulcus can be detected in eye blinking task (A). Activation of bilateral sensorimotor area and bilateral supplementary motor area can be detected in lip pursing task (B). Color bar shows the *t* value.

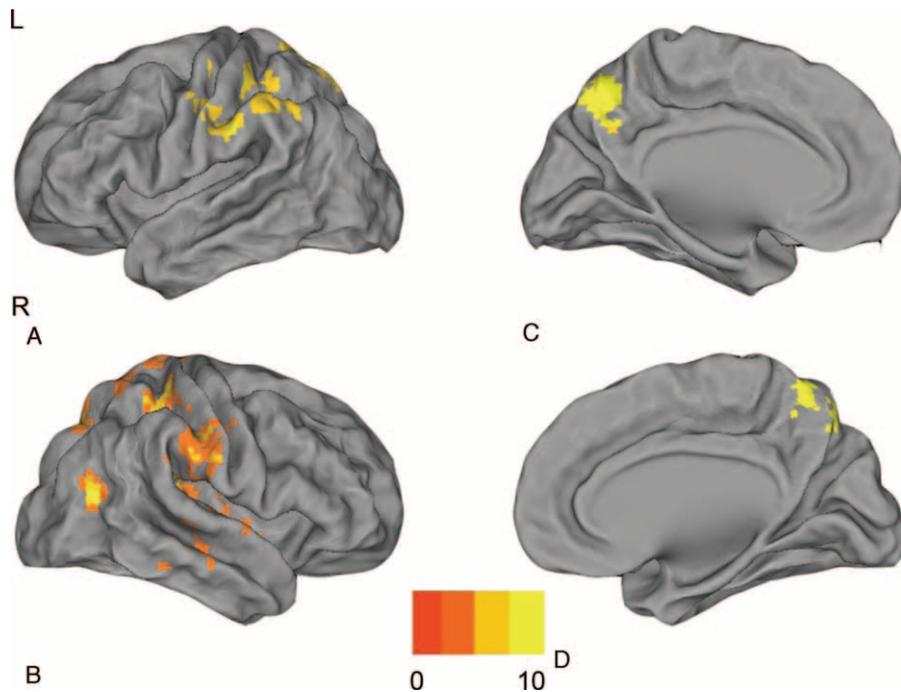


FIGURE 2. For the patients suffered from facial nerve injury of less than 6 months, increased activation in bilateral postcentral gyrus and bilateral inferior parietal lobe was detected in the eye blinking task results as compared with the healthy control group (A and B) and increased activation in bilateral precuneus lobe was observed in the lip pursing task results as compared with the healthy control group (C and D). Color bar shows the *t* value.

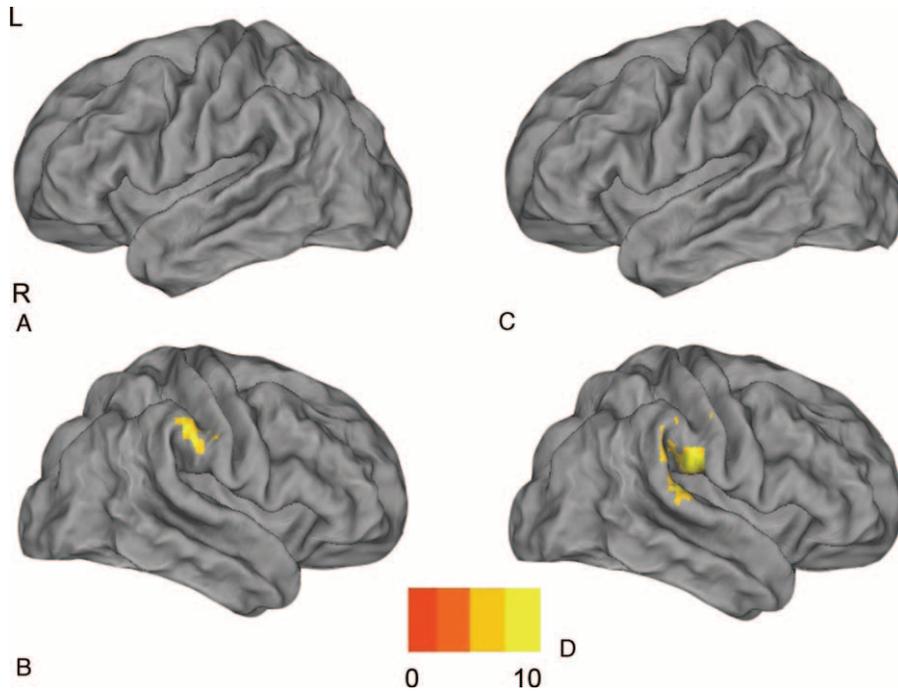


FIGURE 3. For the patients suffered from facial nerve injury of more than 6 months and less than 1 year, increased activation in right supramarginal gyrus was detected in both the eye-blinking and lip-pursing task results as compared with the healthy control group (B and D). Color bar shows the *t* value. While there were no significant differences in both task results as compared with the healthy control group in the left cerebral hemisphere (A and C).

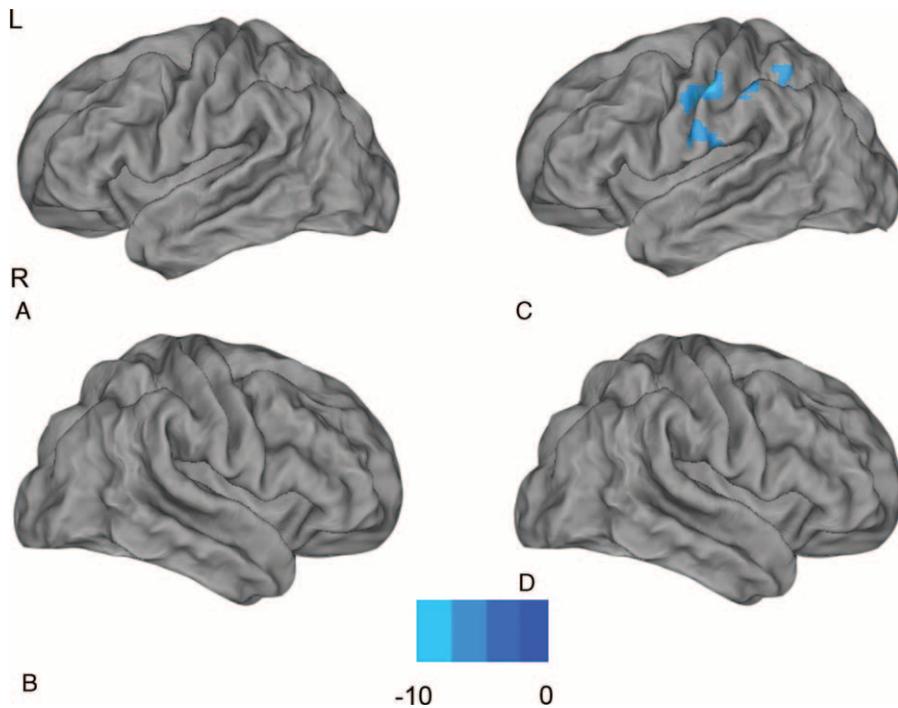


FIGURE 4. For the patients suffered from facial nerve injury of more than 1 year and less than 2 years, decreased activation in left sensorimotor area was observed in the lip pursing task results as compared with the healthy control group (C). While there were no significant differences in the eye blinking task results as compared with the healthy control group (A and B). Also there were no significant differences in the lip pursing task results as compared with the healthy control group in right cerebral hemisphere (D). Color bar shows the *t* value.

TABLE 2. Increased or Decreased Activation in 3 Groups of Facial Nerve Injury Relative to Normal Healthy Group, With a Threshold False Discovery Rate (FDR) Corrected Value of $P=0.01$

Group	Task	Brain Cortex	MNI Coordinates	Cluster Size	T Value
FNI1 group compared with normal healthy group	Eye blinking	Left postcentral gyrus	-60, -27, 33	131	4.25
		Right postcentral gyrus	33, -39, 45	239	5.21
		Left inferior parietal lobe	-18, -42, 51	122	3.73
		Right inferior parietal lobe	42, -66, 15	91	5.42
		Left precuneus lobe	6, -75, 48	190	4.99
FNI2 group compared with normal healthy group	Eye blinking	Right supramarginal gyrus	57, -27, 39	77	4.67
	Lip pursing	Right supramarginal gyrus	57, -24, 27	153	5.76
FNI3 group compared with normal healthy group	Lip pursing	Left precentral gyrus	-63, -15, 45	185	-4.74

FNI1 = patients suffered from facial nerve injury of less than 6 mos, FNI2 = patients suffered from facial nerve injury of more than 6 mos and less than 1 y, FNI3 = patients suffered from facial nerve injury of more than 1 y and less than 2 y, MNI = Montreal Neurological Institute.

eye-blinking and the lip-pursing task results as compared with the healthy control group (Fig. 3B and D). Additionally, there were no significant differences in both task results as compared with the healthy control group in the left cerebral hemisphere (Fig. 3A and C). For the FNI3 group, decreased activation in the left sensorimotor area was observed in the lip-pursing task results as compared with the healthy control group (Fig. 4C). Increased or decreased activation in the 3 groups of facial nerve injury relative to normal healthy group was shown in Table 2.

$Y = 10.086 - 0.463X$, with curve fitting in Figure 5A. Significant correlation was detected between Z value in the right sensorimotor area in the lip-pursing task results and intervals of facial nerve injury, with Pearson correlation coefficient of 0.333 ($P = 0.025$). The fitted regression equation between Z value in the right sensorimotor area (Y) and intervals of facial nerve injury (X) was as following ($P < 0.001$, $R^2 = 64.1\%$, $n = 45$): $Y = 12.063 - 1.29X + 0.139X^2 - 0.004X^3$, with curve fitting in Figure 5B.

Correlation Analysis and Curve Fitting

Significant correlation was found between Z value in the left sensorimotor area in the lip-pursing task results and intervals of facial nerve injury, with Pearson correlation coefficient of $-0.951 (P < 0.001)$. The fitted regression equation between Z value in the left sensorimotor area (Y) and intervals of facial nerve injury (X) was as follows ($P < 0.001$, $R^2 = 90.5\%$, $n = 45$):

DISCUSSION

Increased or Decreased Activation Among Different Intervals of Facial Nerve Injury Patients Compared With Healthy Control Group

Different changes in reorganization were found in different intervals of facial nerve injury patients as compared with the

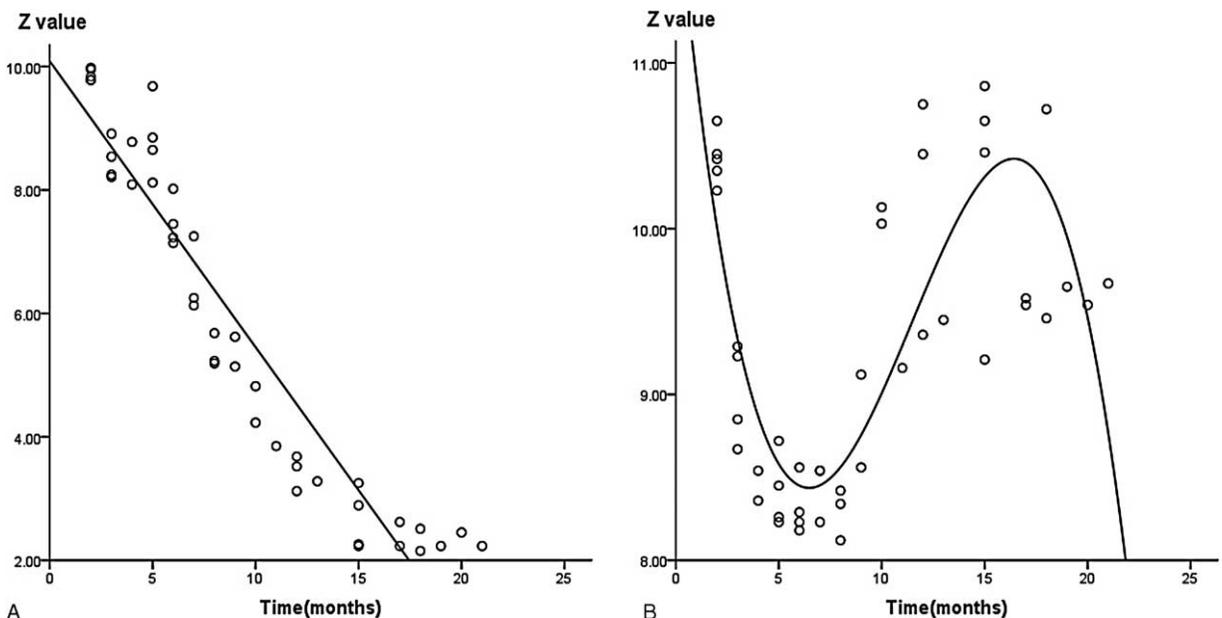


FIGURE 5. Curve fitting between Z value in left sensorimotor area (Y) and intervals of facial nerve injury (X) (A) with the fitted regression equation $Y = 10.086 - 0.463X$ ($P < 0.001$, $R^2 = 90.5\%$, $n = 45$). Curve fitting between Z value in right sensorimotor area (Y) and intervals of facial nerve injury (X) (B), with the fitted regression equation $Y = 12.063 - 1.29X + 0.139X^2 - 0.004X^3$ ($P < 0.001$, $R^2 = 64.1\%$, $n = 45$).

healthy control participants. It is suggested the functional reorganization after facial palsy is dynamic and time-dependent.

For the early group (ie, the FNI1 group), increased activation in bilateral postcentral gyrus and bilateral inferior parietal lobe was detected in the eye-blinking task results as compared with the healthy control group (Fig. 2A and B). The increased activation in the bilateral primary sensory cortex suggests more sensory perception is involved in the early stage of facial dysfunction to perform eye blinking in a precise manner.²³ Additionally, the facial expression is performed based on the symmetry of a face, which is maintained by the intactness of sensorimotor circuit.²⁴ Facial nerve injury could cause damage to the symmetry of face, resulting in destroying the intactness of the sensorimotor circuit. Increased activation in bilateral primary sensory cortex could serve as a mechanism for maintaining this symmetry and overcome impaired movement in facial dysfunction.²⁵ The inferior parietal lobe is a supramodal motor integration area in various movements.²⁶ Also, increased activity in this area in the early stage of facial nerve injury indicates a significant role of the inferior parietal lobe in supramodal motor integration during eye blinking. The precuneus lobe also plays a key role in supermodel integrated tasks, including visuospatial imagery, episodic memory retrieval, and self-processing operations.²⁷ Previous studies have reported that the precuneus lobe has a higher state of activation during motor imagery than during execution of movements.²⁸ Increased activation in the precuneus lobe in the early stage of facial nerve injury in lip-pursing task results (Fig. 2C and D) might be attributable to patients' concern about their facial expression inability, leading to reactivate the imagery of the precise manner of facial movement.²⁷

For the middle group (ie, the FNI2 group), increased activation in right supramarginal gyrus was detected in both task results as compared with the healthy control group (Fig. 3B and D). The supramarginal gyrus is the center of the sensorimotor integration, which has many neuronal connections with other parts of cortexes.¹² The increased activation in the supramarginal gyrus also suggests more sensorimotor integration is involved in the middle stage of facial nerve injury to perform facial movements in a precise manner. Also, the important role of the sensorimotor integration in facial movements is inferred. All patients in this study had facial dysfunction in the right side. In the early stage of facial nerve injury, increased activity could be found in both cerebral hemispheres as compared with healthy individuals (Fig. 2). In the middle stage of facial nerve injury, the increased activation could only be detected in the right cerebral hemisphere, whereas there was no increased or decreased activation in the left cerebral hemisphere as compared with the healthy individuals (Fig. 3A and C), which indicates the potential activation changes within the left cerebral hemisphere due to the right facial dysfunction in the middle stage of facial nerve injury.

For the late group (ie, FNI3 group), decreased activation in the left sensorimotor area was observed in the lip-pursing task results as compared with the healthy control group (Fig. 4C). The left precentral gyrus is the cortex responsible for direct innervation of the right facial, and neurons within the left precentral gyrus serve its dendrite as a pyramidal tract, forming the synapse with the right facial nucleus.²² Long term of incomplete regeneration and transneuronal degeneration within the cortex after right facial nerve injury might result in reduced responses in the left precentral gyrus,^{29,30} which is represented

by decreased activation in the FNI3 group compared with the healthy control group.

The Correlation Between Activation in Bilateral Sensorimotor Area and Intervals of Facial Nerve Injury

Negative correlation and curve fitting (Fig. 5A) between Z value in the left sensorimotor area in the lip-pursing task results and intervals of facial nerve injury suggested progressively attenuated activity in the left sensorimotor area after the occurrence of facial dysfunction (Fig. 5A). In our study, all patients had facial nerve injury in the right side. The motor neurons that innervate the oral muscles in right face receive a purely input from the left sensorimotor cortex. The progressively attenuated activity in the left sensorimotor area indicates that dysfunction in the facial nerve has devastating effects on the contralateral sensorimotor area.^{7,8} Curve fitting (Fig. 5B) between Z value in the right sensorimotor area in the lip-pursing task results and intervals of facial nerve injury revealed that the activation in the right sensorimotor area was reduced in early stage of facial dysfunction (ie, less than 6 mos, Fig. 5B), whereas the activation was gradually enhanced by 6 to 17 months (Fig. 5B), and the activation was reduced once more in late stage of facial dysfunction (ie, 17 mos later; Fig. 5B). The attenuated intensity in the right sensorimotor area in the early stage indicates that dysfunction in facial nerve also has devastating effects on the ipsilateral sensorimotor area, and the enhanced intensity in the middle stage suggests the possible interhemispheric reorganization involvement in facial movements.^{5,23} Whereas the reduced intensity in the late stage indicates the devastating effects on the ipsilateral sensorimotor area due to the long-term pathology of facial nerve injury. Thus, dysfunction in facial nerve has devastating effects on the sensorimotor area in the early and late stages, whereas enhanced intensity in the ipsilateral sensorimotor area in the middle stage of facial nerve injury suggests possible interhemispheric reorganization involvement.

Generalizability

In our study, 2-sample *t* tests were used to test for areas of increased or decreased activation in the 3 facial nerve injury groups relative to the normal healthy group. And the results were obtained by the software xjView in SPM8 (<http://www.a-livetrain.net/xjview/ad.php>) at a threshold FDR corrected value of $P = 0.01$. As for 2-sample *t* tests in fMRI, FDR corrected had greater power and efficiency than FWE-corrected.¹⁹ Also, xjView is a useful tool to find out the anatomical name of the selected voxel or clusters, and to display cluster's anatomical information and list all cluster information.²⁰ As for the correlation analysis between intensity of bilateral sensorimotor areas and interval after facial nerve injury, FWE-corrected was used to determine the activation intensity in the sensorimotor area, namely the Z value. Because the activation intensity in the sensorimotor area was obtained from fMRI data of every participant, so the statistical criterion should be more rigorous and the FWE-corrected was used.^{21,22}

Limitations

A prospective study on the same patient cohort at different time after injury (eg, 3, 6, 12, 18, and 24 mos) would, however, be more robust to investigate the changes of brain fMRI signal with time. This is a limitation of the study design of using 3

groups of patients at different disease stages, and it is difficult to study the same group of patients at different time after facial nerve injury, especially for a long time (eg, 12 or 24 mos). Also, the patients were asked to perform bilateral facial motion task; therefore, it is hard to conclude that whether the enhanced intensity in the right sensorimotor area is resulted from the involvement of left face due to the right facial nerve injury or not. This is another limitation of the study design. It would be interesting to have a motor task design of unilateral face motion to verify whether the enhanced right intensity is indeed a compensation when right face is asked to move, just as the task design of unilateral limb movements in spinal cord injury.^{31,32} But in facial nerve injury, it is difficult to have a motor task design of unilateral face motion, especially for patients who had complete facial dysfunction with HBS in the range of 5 to 6.

CONCLUSIONS

Functional reorganization after facial nerve injury is both dynamic and time-dependent. Both the supramodal motor integration and sensorimotor integration play a significant role in facial movements, and increased activation in integration areas, such as supramarginal gyrus and precunes lobe, could be detected in the early-middle stage of facial dysfunction compared with normal individuals. Decreased activation in the sensorimotor area contralateral to facial nerve injury could be found in the late stage of facial dysfunction compared with normal individuals. Dysfunction in the facial nerve has devastating effects on the sensorimotor areas, whereas enhanced intensity in the sensorimotor area ipsilateral to facial nerve injury in middle stage of facial dysfunction suggests the possible involvement of interhemispheric reorganization. Behavioral or brain stimulation techniques treatment in this stage could be applied to alter reorganization within sensorimotor area in the rehabilitation of facial function, monitoring of therapeutic efficacy, and improvement in therapeutic intervention along the course of recovery.

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