

SPONTANEOUS NEURAL ACTIVITY ALTERATIONS IN TEMPOROMANDIBULAR DISORDERS: A CROSS-SECTIONAL AND LONGITUDINAL RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

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Abstract—The involvement of the central nervous system in the pathophysiology of temporomandibular disorders (TMD) has been noticed. TMD patients have been shown dysfunction of motor performance and reduced cognitive ability in neuropsychological tests. The aim of this study is to explore the spontaneous neural activity in TMD patients with centric relation (CR)–maximum intercuspation (MI) discrepancy before and after stabilization splint treatment. Twenty-three patients and twenty controls underwent clinical evaluations, including CR–MI discrepancy, Helkimo indices and chronic pain, and resting state functional magnetic resonance imaging scans at baseline. Eleven patients repeated the evaluations and scanning after the initial wearing (T1) and 3 months of wearing (T2) of the stabilization splint. The fractional amplitude of low-frequency fluctuation (fALFF)

was calculated to compare the neural functions. At baseline, the patients showed decreased fALFF in the left precentral gyrus, supplementary motor area, middle frontal gyrus and right orbitofrontal cortex compared with the controls ($P < 0.05$, AlphaSim corrected). Negative correlations were found between the fALFF in the left precentral gyrus and vertical CR–MI discrepancy of bilateral temporomandibular joints of patients ($P < 0.05$, two-tailed). At T2, the symptoms and signs of the patients were improved, and a stable condylar position on the CR was recovered, with increased fALFF in the left precentral gyrus and left posterior insula compared with pretreatment. The fALFF decrease in the patients before treatment was no longer evident at T2 compared with the controls. The results suggested that TMD patients with CR–MI discrepancy showed significantly decreased brain activity in their frontal cortexes. The stabilization splint elicited functional recovery in these cortical areas. These findings provided insight into the cortical neuroplastic processes underlying TMD with CR–MI discrepancy and the therapeutic mechanisms of stabilization splint. © 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: temporomandibular disorders, centric relation, chronic pain, functional magnetic resonance imaging, neuroplasticity, occlusal splints.

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Abbreviations: Ai, anamnestic dysfunction index; BOLD, blood oxygen level-dependent; CR–MI discrepancy, centric relation–maximum intercuspation discrepancy; Di, clinical dysfunction index; DPARSF, Data Processing Assistant for Resting-State fMRI; fALFF, fractional amplitude of low-frequency fluctuation; fMRI, functional magnetic resonance imaging; GCPS, Graded Chronic Pain Scale; MRI, magnetic resonance imaging; RDC/TMD, Research Diagnostic Criteria for Temporomandibular Disorders; rfMRI, resting state functional magnetic resonance imaging; TMD, temporomandibular disorders; TMJ, temporomandibular joint.

INTRODUCTION

Temporomandibular disorders (TMD) are defined as a subgroup of craniofacial pain problems involving the temporomandibular joint (TMJ), masticatory muscles and associated head and neck musculoskeletal structures. TMD patients most frequently suffer from fairly localized pain, limited or asymmetric mandibular movements and TMJ noises and other common associated symptoms include ear pain and stuffiness, tinnitus, dizziness, neck pain, and headache. (Scrivani et al., 2008). TMD is a common reason for chronic facial pain and the prevalence of TMD has been reported to vary from 7% to 84% in different studies (Luther, 2007). The signs and symptoms could be chronic and difficult to manage and thus the oral health-related quality of life was negatively affected in TMD patients (John et al., 2007; Dahlstrom and Carlsson, 2010). Besides, there is a marked comorbidity of TMD with fibromyalgia and other chronic pain syndromes and stress-related disorders

(Eze-Nliam et al., 2011). The etiologies and pathogenesis of TMD are poorly understood and are considered multifactorial including systemic, physiological and structural factors (Scrivani et al., 2008). Recently it is considered that TMD may share a common pathophysiology involving the central nervous system similar to disorders such as fibromyalgia and chronic fatigue syndrome (Scrivani et al., 2008). TMD patients have been shown to have abnormal cortical response to tactile stimulation, exhibit dysfunction of motor performance and have reduced cognitive ability in neuropsychological tests (Shibukawa et al., 2007; Nebel et al., 2010; Weissman-Fogel et al., 2011). Although structural and functional neural changes have been reported by a few studies, suggesting an important role of the central nervous system in TMD, further studies are needed to characterize pattern of neural alterations in TMD regarding the complex representations of TMD symptoms and signs (Younger et al., 2010; Moayed et al., 2011; Weissman-Fogel et al., 2011; Ichesco et al., 2012).

Centric relation (CR)–maximum intercuspation (MI) discrepancy, which refers to the shift of condyle between two important physical mandibular positions – CR and MI during mandibular movement, is often observed in TMD patients (He et al., 2010; Weffort and de Fantini, 2010; Barrera-Mora et al., 2012; Padala et al., 2012). CR describes the position of condyles articulating with the thinnest avascular portion of their respective disks with the condyle in the anterior–superior position against the slopes of the articular eminence, which is a position independent of tooth contact. MI describes the complete intercuspation of the opposing teeth independent of the condylar position, and the condylar position in MI is subject to tooth contact. The relationship between the CR–MI discrepancy and TMD is not clearly understood. The current evidences have not excluded the potential relevance of condylar positions to TMD (Rinchuse and Kandasamy, 2005; Mohlin et al., 2007; Scrivani et al., 2008). Functional occlusal theory believes that achieving CR–MI harmony after orthodontic treatment reduces the risk of developing TMD (Williamson, 1976; Roth, 1981; Cordray, 1996). Our previous experiment found that the degree of CR–MI discrepancy has a positive correlation with the severity of the signs and symptoms of TMD, and might serve as a reliable indicator of the presence and severity of TMD (He et al., 2010). A few studies have also suggested displacement between CR and MI may play a significant role in signs and symptoms of TMJ disorders (Weffort and de Fantini, 2010; Barrera-Mora et al., 2012; Padala et al., 2012). Mandibular movement conducted by masticatory systems is of great importance not only for oral-related functions such as food taking and speech, but also for the systematic, mental and physical functions of the body, especially the cognitive function of the brain (Ono et al., 2010). The peripheral sensory inputs from the tooth, oral muscles and TMJ could modulate the mandibular movements, which are generated and dominated by the central nervous system (Onozuka et al., 2002). However, the spontaneous neural function of TMD patients with CR–MI discrepancy has not previously been explored.

Functional magnetic resonance imaging (fMRI) is a non-invasive technique to demonstrate brain functional activity by using blood oxygen level-dependent (BOLD) signals (Biswal et al., 1995). Previous fMRI studies have revealed abnormal motor and cognitive functions in TMD patients during specific tasks (Nebel et al., 2010; Weissman-Fogel et al., 2011; Ichesco et al., 2012). Resting state fMRI (rfMRI) investigates brain function and is considered to be physiologically meaningful and related to spontaneous neural activity (Fox and Raichle, 2007). The fractional amplitude of low-frequency fluctuation (fALFF) of BOLD signals measures the power of a given time course within a specific frequency range (e.g., 0.01–0.08 Hz) divided by the total power in the entire detectable frequency range, providing a specific measure of intrinsic low-frequency oscillatory phenomena and effectively suppressing non-specific signal components. Therefore, this factor significantly improves the sensitivity and specificity involved in detecting regional spontaneous brain activity (Zou et al., 2008).

To our best knowledge, rfMRI has not been used previously to examine brain functions in TMD patients with CR–MI discrepancy. Furthermore, the stabilization splint has been found to be effective in alleviating TMD symptoms and signs, although little evidence has been shown to illustrate the mechanisms of action (Dawson, 2006; Scrivani et al., 2008). Thus, the aims of the present study were to explore intrinsic neural function in TMD patients with CR–MI discrepancy before and after stabilization splint treatment using rfMRI. We hypothesized the following that: (i) TMD patients would show abnormal spontaneous neural activity at baseline, which would be associated with CR–MI discrepancy, and (ii) the altered brain activity would become more normal after the treatment.

EXPERIMENTAL PROCEDURES

Participants

This study was approved by the ethics board of Sichuan University, and written informed consent was obtained from all subjects. The inclusion criteria for the patient group (P) were the following: full permanent dentition; no history of orthodontic or prosthetic treatment, injury to the face or jaw, chewing side preference, or rheumatic arthritis; the presence of TMD diagnosed by the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin and LeResche, 1992); with CR–MI discrepancy according to the criteria of discrepancy > 1 mm in the horizontal or vertical planes and/or > 0.5 mm in the transverse plane. (Crawford, 1999); and being right-handed. No patients took any drugs for TMD before the first rfMRI scanning, and no patients took any other treatments except stabilization splint during the whole follow-up. The inclusion criteria for the healthy control group (N) were the following: full permanent dentition; no history of orthodontic or prosthetic treatment, injury to the face or jaw, chewing side preference, parafunction or rheumatic arthritis; no signs and symptoms of TMD according to RDC/TMD criteria; CR–MI in harmony; and being right-handed. All

participants in the present study were screened using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Non-Patient Edition, and they had no history of psychiatric illness in first-degree relatives. Twenty-three patients and twenty healthy controls were involved in the present study. Demographic variables were not significantly different between the patients and controls (Table 1).

The exclusion criteria for both groups included the following: any neurological disorders, neurosurgery, current or past substance abuse or dependence, pregnancy, significant systemic illness and MR contraindications including cardiac pacemakers and other metallic implants. Diagnostic quality MR images were inspected by two experienced neuroradiologists to exclude subjects with any gross abnormalities.

Clinical measures

The psychosocial assessments of depressive and non-specific physical symptoms (somatization) were evaluated for all the participants according to RDC/TMD axis II which is based on the Symptom Checklist 90-R (SCL-90-R) depression and somatization scales. The characteristics of chronic pain including pain duration and Graded Chronic Pain Scale (GCPS) that consists of Characteristic Pain Intensity and Disability Points were recorded according to the RDC/TMD axis II for TMD patients. The Helkimo indices were calculated including the anamnestic dysfunction index (Ai) and the clinical dysfunction index (Di), to determine the severity of the signs and symptoms of TMD patients (Helkimo, 1974).

The records and measurements of CR–MI discrepancy in three dimensions were performed as previously reported (He et al., 2010) for all the participants (Fig. 1A–E). The measurement was performed by one operator blinded to the TMJ status of the subjects. The reproducibility of the measurements was assessed by repeating the measurements 2 weeks apart in 20 randomly selected samples (ten for each group) and was calculated using Dahlberg's equation for method error: $ME = \sqrt{\sum D^2 / 2N}$ where D is the difference between duplicated measurements and N is the number of repeated measurements. The errors were low being 0.01 mm for the discrepancy in the horizontal and transverse planes and 0.02 mm for the vertical plane, suggesting a high reproducibility.

Stabilization splint treatment

Eleven out of the 23 patients were under the stabilization splint treatment, completed the clinical and rfMRI re-examination and formed the treatment group (T) with a longitudinal follow-up. An anterior deprogramming splint which allows contacts of the lower anterior teeth against a smooth flat surface was made and worn except when eating and tooth brushing for 2 weeks in all the samples to relieve the symptoms and signs of muscle pain, to confirm a diagnosis of occluso-muscle disorder and to help seating the condyle into the proper CR. The maxillary stabilization splints (Fig. 1F) were then fabricated on casts mounted in the CR and were worn 24 h a day for 3 months except when tooth brushing. The stabilization splint should fit the upper arch, be easy to wear and have enough retention. Equal contact of the lower teeth against a smooth splint surface should be achieved when the joint is completely seated in the CR. The splint should have an anterior guidance ramp angled to be as shallow as possible for free horizontal mandibular movement and to allow immediate disocclusion of the posterior teeth. The splint must be checked every month to ensure that the splint is functioning well. If there was an adjustment of the condylar position within the first few days, the measurement of CR–MI discrepancy would be repeated and the stabilization splint would be adjusted or re-fabricated. The treatment group ($n = 11$) underwent the assessment of TMJ and magnetic resonance imaging (MRI) scan three times, which were at pre-treatment (T0), initial wearing of the stabilization splint within 24 h (T1) and 3 months after the stabilization splint (T2). Because previous studies indicated a high level of consistency over time in the resting state measurements in healthy individuals, the controls in the present study were scanned only once at the baseline to define the range of normal function (Harrison et al., 2008; Shehzad et al., 2009; Lui et al., 2010).

MR data acquisition

All subjects underwent an rfMRI scan using a 3T Siemens Trio MRI system with an 8-channel phased-array head coil. BOLD-sensitive MR images were obtained with a gradient-echo echo-planar imaging (EPI) sequence: repetition time/echo time (TR/TE), 2000/30 ms; flip angle, 90°; slice thickness, 5 mm without intersection

Table 1. Demographic information and clinical measures of all the participants at baseline

	Patient group ($n = 23$)	Control group ($n = 20$)	<i>P</i> value
Age (year, mean \pm SD)	22.4 \pm 3.6	23.1 \pm 2.4	0.471
Gender (male/female)	9/14	9/11	0.697
Height (mm, mean \pm SD)	166 \pm 7.1	165 \pm 7.9	0.588
Weight (kg, mean \pm SD)	54.7 \pm 7.8	57.2 \pm 9.8	0.344
Education duration (year, mean \pm SD)	16.5 \pm 3.0	17.5 \pm 1.3	0.148
SCL-Depression ^a score (mean \pm SD)	0.19 \pm 0.24	0.10 \pm 0.10	0.095
SCL-Somatization ^b score (mean \pm SD)	0.22 \pm 0.20	0.15 \pm 0.12	0.112

^a SCL-Depression, Symptom Checklist 90-R depression scale.

^b SCL-Somatization, Symptom Checklist 90-R somatization scale.

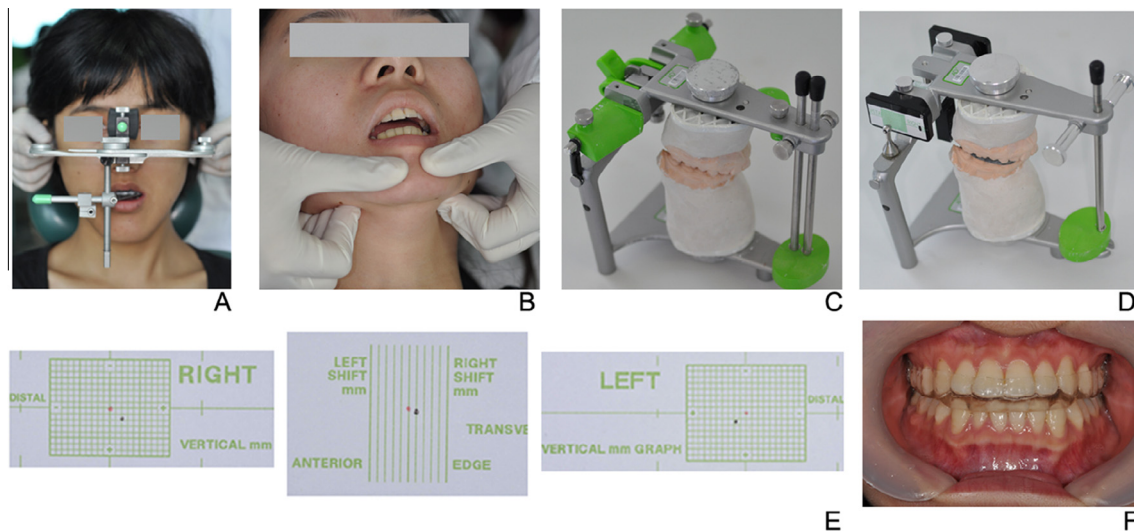


Fig. 1. Measurement of the CR–MI discrepancy. (A) A face-bow record of the maxillary position was taken; (B) The CR position was determined by the bimanual manipulation technique and recorded; (C) The maxillary and mandibular cast were mounted in the CR and MI; (D) The mounted diagnostic casts were subsequently transferred to the condylar position indicator; (E) The three dimensional differences in the condylar position between the CR and MI of the left and right joints were measured; (F) The stabilization splint in a month.

gaps; matrix size, 64×64 ; field of view, $240 \times 240 \text{ mm}^2$; and voxel size, $3.8 \times 3.8 \times 5 \text{ mm}^3$. Each brain volume comprised 30 axial slices, and each functional run contained 180 image volumes. During scanning, the subjects were instructed to relax with their eyes closed without falling asleep, without directed, systematic thought (confirmed by subjects immediately after the experiment), and with the mouth closed and mandible in a resting position without the tooth touching. The treatment group wore the stabilization splint during the second and the third scans.

Data preprocessing and fALFF calculation

Functional image preprocessing was conducted using SPM8 and the Data Processing Assistant for Resting-State fMRI (DPARSF) software (Chao-Gan and Yu-Feng, 2010). For each participant, the first 10 volumes were discarded to allow for scanner stabilization and subject familiarization, and the remaining images were corrected for different signal acquisition times by shifting the signal measured in each slice relative to the middle volume, followed by realignment using a six-parameter (rigid body) linear transformation. In the present study, head translation movement for all participants was $< 1.5 \text{ mm}$, and rotation was $< 1.5^\circ$; the head motion effects (six motion parameters) were regressed out. The analysis of head motion parameters did not reveal differences in the motion correction parameters between any pair of groups, and no subjects were excluded for excessive head motion. The signals from the white matter and cerebrospinal fluid were regressed out. In addition, linear trends were also included as regressors as the BOLD signal demonstrates low-frequency drifts. Then, the images were spatially normalized to the Montreal Neurological Institute template, and each voxel was resampled to $3 \times 3 \times 3 \text{ mm}^3$, and then a spatial smoothing transformation

was conducted with an 8-mm full width half-maximum Gaussian kernel.

The fALFF values were calculated using DPARSF software based on previous study (Zou et al., 2008). The time series for each voxel was transformed to the frequency domain without band-pass filtering and the power spectrum was obtained. Because the power of a given frequency is proportional to the square of the amplitude of this frequency component, the square root was calculated at each frequency of the power spectrum. fALFF is the ratio of the sum of the amplitude across the low-frequency band (0.01–0.08 Hz) to the sum of the amplitudes across the entire frequency range detectable in a given signal. Then with the standardization procedure, the individual fALFF map was normalized by the individual's global mean fALFF.

Statistical analysis

The differences in age, height, weight, education, depression and somatization between patient and control groups were obtained with two-sample *t*-test using SPSS (Statistical Package for the Social Sciences) version 16.0 software. The comparison of sex-ratio was performed using the chi-square test. The differences of Di in patients at different time points were examined by the paired-sample *t*-test. The analyses of the fALFF differences were performed in SPM8 between (i) the patient and control groups using a two-sample *t*-test at baseline, (ii) the treatment group at T0 vs. T1 and T0 vs. T2 using a paired-sample *t*-test, and (iii) the treatment group at T2 and the control group using a two-sample *t*-test; statistical significance was set at $P < 0.05$ after AlphaSim correction (combined $P < 0.001$ uncorrected at the cluster level and minimum cluster size of nine voxels) for multiple comparisons. The coordinates are reported in Talairach space after

conversion from Montreal Neurological Institute space using mni2tal.m. The two-tailed Pearson correlation analyses were performed to assess the relationship between the clinical measures and fALFF values before and after the treatment.

RESULTS

Clinical measures

The depressive and somatization scores in the patient and control groups showed no significant differences (Table 1). There were two patients with moderate depression and four patients with moderate somatization (Table 2), and the remaining patients and 20 controls were all at normal level, suggesting that the psychosocial state might not be the critical causative factor for TMD in the present study. Twelve out of 23 patients had chronic pain, including seven patients with low disability and low pain intensity classified as Grade I and 5 patients with low disability and high pain intensity classified as Grade II (Table 2). The mean pain duration (\pm standard deviation) is 14.8 ± 20.7 months, with chronic pain intensity of 47.3 ± 21.4 and disability points of 24.5 ± 16.2 .

The condylar positions in the MI were dislocated from the CR in an anterior–inferior direction with transverse deviations in all TMD patients with CR–MI discrepancy before treatment (Table 3). The Ai and Di of TMD patients are shown in Table 4. After the splint treatment, fewer patients had a high degree of Di, and the mean score of Di at T1 and T2 was significantly decreased compared with that at T0 ($t = 2.666$, $P = 0.024$ and $t = 5.584$, $P < 0.001$, respectively), revealing an improvement in the TMJ status after treatment. At T1, none of the 11 patients had any spontaneous pain, but the occlusion was not stable. At T2, the 11 patients had no pain on palpation or during any mandibular movement and exhibited a larger range of mandibular motion. The TMJ noises during movement were absent or decreased. The patients could bite on the CR easily, repeatedly and comfortably with or without the splint in

place, suggesting that a stable condylar position on the CR was recovered and adapted by the patients.

Regional neural function before treatment (cross-sectional study)

At baseline, the TMD patients with CR–MI discrepancy showed decreased fALFF in the left precentral gyrus (primary motor cortex), left supplementary motor area, left middle frontal gyrus and right orbitofrontal cortex relative to the controls ($P < 0.05$ AlphaSim corrected) (Fig. 2 and Table 5). There were no areas showing significantly increased fALFF in the patients compared with the controls. There was no significant difference in the fALFF between TMD patients with and without chronic pain and there was no correlation between the fALFF and pain duration, characteristic pain intensity or disability points in patient group. In the patient group, a negative correlation was found between the fALFF of the left precentral gyrus and the vertical CR–MI discrepancy (for the left joint, $r = -0.425$, $P = 0.045$; for the right joint, $r = -0.580$, $P = 0.004$, two-tailed) (Fig. 3).

Improved regional neural function in the treatment group (longitudinal study)

At T1 with the initial wearing of the stabilization splint, the fALFF in the patients was not significantly different compared with that at pretreatment, demonstrating that the treatment with the anterior deprogramming splint and the increased bite height raised by the stabilization splint did not affect the intrinsic brain activity.

After 3 months of treatment with the stabilization splint at T2, the patients showed increased fALFF in the left precentral gyrus and left posterior insula relative to the pretreatment (Fig. 2 and Table 5). The decreased fALFF in the patients before treatment were no longer evident at T2 compared with the controls, while a lower fALFF was observed in the left postcentral gyrus and right superior parietal lobule of the patients at the T2 follow-up (Fig. 2 and Table 5).

Table 2. Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) axis II diagnoses in patients with temporomandibular disorders

RDC/TMD axis II diagnoses		Patient numbers (%)
GCPS ^a	0	11 (48%)
	I	7 (30%)
	II	5 (22%)
	III	–
	IV	–
SCL-Depression ^b	Normal	21 (91%)
	Moderate	2 (9%)
	Severe	–
SCL-Somatization ^c	Normal	19 (83%)
	Moderate	4 (17%)
	Severe	–

^a GCPS, Graded Chronic Pain Scale; Grade 0, no chronic pain; Grade I, low disability, low pain intensity; Grade II, low disability, high pain intensity; Grade III, high disability, moderately limiting; Grade IV, high disability, severely limiting.

^b SCL-Depression, Symptom Checklist 90-R depression scale.

^c SCL-Somatization, Symptom Checklist 90-R somatization scale.

DISCUSSION

Although a clear pattern of neural alterations in TMD has not been determined, previous MRI studies have found abnormal gray matter volume and thickness mainly in the frontal regions including the primary motor cortex, orbitofrontal cortex and dorsolateral prefrontal cortex (Younger et al., 2010; Moayed et al., 2011), and altered functional activity and connectivity between these frontal areas and cortical-subcortical regions (Nebel et al., 2010; Weissman-Fogel et al., 2011; Ichescio et al., 2012). In the present study, we found decreased intrinsic neural activity in the left primary and supplementary motor area and the middle- and orbital-frontal cortex of TMD patients (Fig. 2 and Table 5), revealing the effects of illness on neural systems with functional abnormalities. Neurocognitive and neuroimaging studies have established the notion that the primary and supplementary motor areas are associated with sensorimotor control

Table 3. Three dimensional centric relation–maximum intercuspation discrepancy in left and right joints of patients with temporomandibular disorders before treatment

	Centric relation–maximum intercuspation discrepancy				
	Vertical		Horizontal		Transverse
	Left joint	Right joint	Left joint	Right joint	
Patient numbers (%)	15(65%)	16(70%)	15(65%)	14(70%)	9(39%)
Mean \pm SD (mm)	1.8 \pm 1.5	1.9 \pm 1.5	1.3 \pm 0.9	1.0 \pm 0.6	0.4 \pm 0.2
Range (mm)	0.0–5.0	0.0–5.0	0.0–3.2	0.0–2.0	0.0–1.0

Table 4. Helkimo index in patients with temporomandibular disorders at baseline and follow-up

	Helkimo index								Score (Mean \pm SD)	Analyses	
	Ai ^a			Di ^b				Score			Analyses
	0	I	II	0	I	II	III				
P ^c (n = 23)		5(22%)	18(78%)		7(30%)	7(30%)	9(39%)	7.74 \pm 4.92			
T0 ^d (n = 11)		1(9%)	10(91%)		2(18%)	3(27%)	6(55%)	9.82 \pm 5.13			
T1 ^e (n = 11)					2(18%)	5(46%)	4(36%)	8.09 \pm 4.21	P = 0.024 (T0 vs. T1)		
T2 ^f (n = 11)					2(18%)	6(55%)	3(27%)	2.0 \pm 2.0	P < 0.001 (T0 vs. T2)		

^a Ai, the anamnestic dysfunction index.

^b Di, the clinical dysfunction index.

^c P, patient group at baseline.

^d T0, treatment group before treatment.

^e T1, treatment group after initial wearing of stabilization splint.

^f T2, treatment group after three-month treatment of stabilization splint.

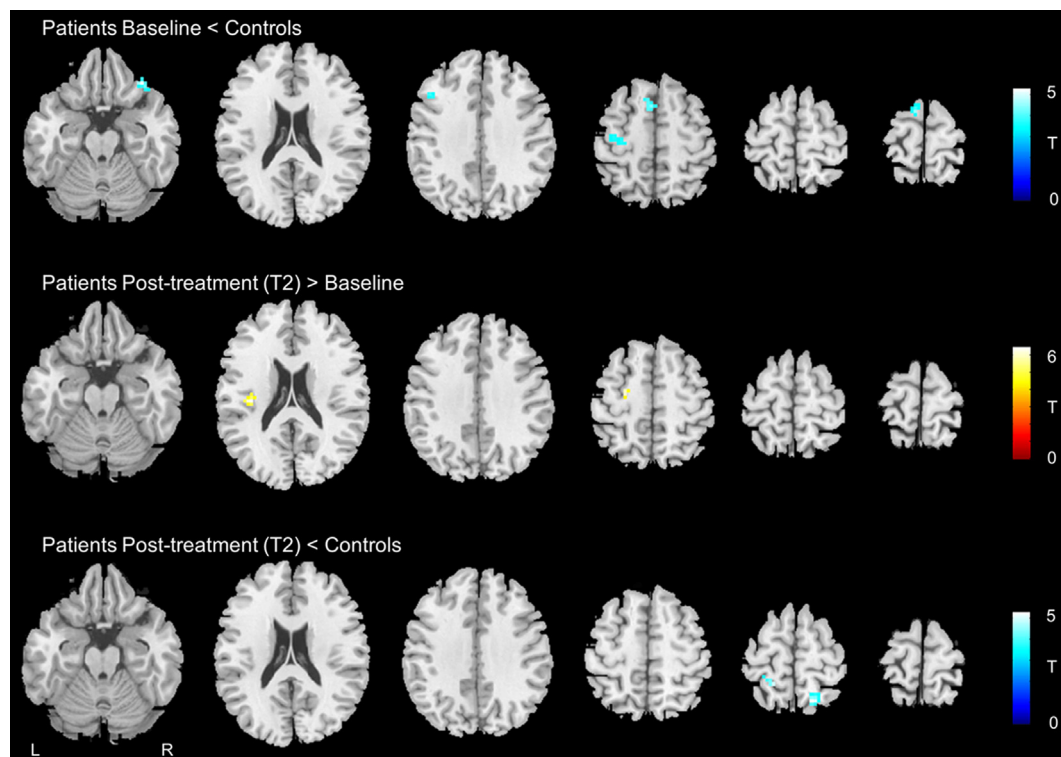


Fig. 2. Images showing the results of the fractional amplitude of low-frequency fluctuation (fALFF) analysis. Upper panel: compared with the controls, the TMD patients showed a decreased fALFF (blue) in the left precentral gyrus, left supplementary motor area, left middle frontal gyrus and right orbitofrontal cortex. Middle panel: compared with the baseline, the patients showed increased fALFF (yellow) in the left precentral gyrus and left posterior insula after 3 months of treatment. Lower panel: compared with the controls, the patients showed decreased fALFF (blue) in the right superior parietal lobule and left postcentral gyrus after 3 months of treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5. Brain areas that showed significant changes in fALFF between patients and controls and between baseline and post-treatment in temporomandibular disorders patients with CR–MI discrepancy

Brain area	BA ^a	Talairach			Number of voxel	t Value
		x	y	z		
<i>Baseline: patients < controls</i>						
Left precentral gyrus	4	−38	−15	56	20	−3.74
Left supplementary motor area	6	−9	6	66	17	−4.47
Left supplementary motor area	6	−3	14	52	16	−4.29
Left middle frontal gyrus	10	−45	22	32	10	−3.87
Right orbitofrontal cortex	47	30	17	−19	15	−5.27
<i>Post-treatment (T2^b) > baselines (T0^c)</i>						
Left precentral gyrus	6	−24	−9	53	9	5.99
Left posterior insula	13	−36	−19	20	16	6.46
<i>Post-treatment (T2^b) < controls</i>						
Right superior parietal lobule	7	18	−51	66	27	−5.18
Left postcentral gyrus	5	−20	−43	63	17	−4.76

^a BA, Brodmann area.

^b T2, treatment group after three-month treatment of stabilization splint.

^c T0, treatment group at baseline.

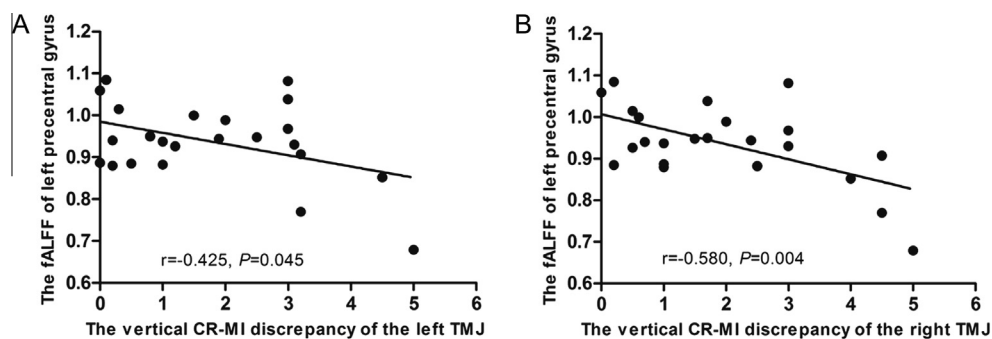


Fig. 3. At the first fMRI assessment before the treatment, there were significant negative correlations (A) between the fALFF of the left precentral gyrus and the vertical CR–MI discrepancy of the left temporomandibular joint ($r = -0.425$, $P = 0.045$, two-tailed) and (B) between the fALFF of the left precentral gyrus and the right temporomandibular joint ($r = -0.580$, $P = 0.004$, two-tailed) in the TMD patient group.

and mandibular movements (Sessle et al., 2007; Haller et al., 2009), and that the orbitofrontal cortex and middle frontal gyrus are involved in cognitive processing including emotion regulation and executive function (Schoenbaum and Roesch, 2005); abnormal functional activity in these regions was reported in TMD patients under task-evoked stimulation (Weissman-Fogel et al., 2011). Consistent with these previous studies, the TMD patients with CR–MI discrepancy demonstrated not only a functional deficit in the primary and supplementary motor regions but also dysfunction in cognition-related brain areas in the present study, suggesting that the frontal cortex has a critical role in the pathophysiology of TMD.

Furthermore, we found a negative correlation between the vertical CR–MI discrepancy and the fALFF in the left primary motor cortex in TMD patients (Fig. 3). The more the condylar deviated from the CR vertically, the more the fALFF value in the precentral gyrus decreased, highlighting a CR–MI discrepancy-based pathophysiological process in TMD. However, there were no associations between the altered neural activity and the horizontal or transverse discrepancy, which might be

due to a more critical role of vertical discrepancy in TMJ signs and symptoms, as suggested by a previous study (Barrera-Mora et al., 2012).

Some previous MRI studies found functional alterations in areas such as insula and cingulate cortex in chronic pain TMD, suggesting the contribution of chronic pain to abnormal brain function (Gerstner et al., 2012; Ichesco et al., 2012). However, the results in this study did not show abnormal fALFF at baseline in more brain areas that were associated with pain in previous fMRI studies. For the areas with fALFF alterations, there are no significant differences for fALFF between the TMD patients with and without chronic pain and there is no correlation between the fALFF and pain duration, characteristic pain intensity or disability points in chronic pain patients. This may be explained that, firstly, not all the patients participated in this study have chronic myofascial pain, and in the patients with chronic myofascial pain, the pain level is relatively low and the duration is relatively short, and thus the alterations in the sensory cortex may be more variable and not consistent. Also, secondly, before treatment, we found the decreased fALFF correlated with the extent of the CR–MI discrepancy, not with

the pain duration, intensity or disability points, suggesting the important role of CR–MI discrepancy, rather than TMD pain, in the pathophysiology of TMD in the present study. Therefore, the fALFF alterations of pain associated areas in TMD patients, if any, may not be revealed by this current study and needs further studies.

After treatment, compared with the pretreatment, the TMD patients were found to have increased function of the left primary motor cortex and posterior insula (Fig. 2 and Table 5). The cellular and molecular changes in posterior insula have been reported related to TMD symptoms (Gerstner et al., 2012). Compared with the controls at T2, the decreased fALFF in the frontal cortex of the TMD patients before the treatment was shifted toward the normal level after 3 months of stabilization splint treatment and clinical remission.

The functional alterations may reflect the neural plasticity. Neural plasticity is an intrinsic property of the human nervous system, which might be the mechanism for development and learning, and also be a cause of pathology and the cause of clinical disorders (Avivi-Arber et al., 2011). An appropriate sensory input could result in a normal efficient functioning-related neural plasticity, while an abnormal input or abnormality in the brain response to sensory input might interfere with the processing programs in the brain areas, resulting in the development of distorted plasticity (Yin et al., 2007). Occlusal interference has been proven to cause spatial memory and learning ability deficits by altering neural function in animals (Ichihashi et al., 2007; Kubo et al., 2007). The CR–MI discrepancy can cause occlusal interference and interfere with efficient occlusion. According to functional occlusal theory, to bypass these interferences, the masticatory muscle will contract nonphysiologically and the condyle will be dislocated. Abnormal peripheral inputs from the teeth, muscles and the TMJ, therefore, may cause undesired cortical plasticity and functional maladaptation of the sensorimotor system through the neuroplastic capabilities of the sensory and motor cortices (Avivi-Arber et al., 2011). The decreased fALFF may be a functional accompaniment or a biomarker of a decrease in sensory or motor activity that has been affected by CR–MI discrepancy and neural plasticity in these patients at baseline, which is consistent with previous studies reporting decreased neural activity and connectivity in TMD patients (Shibukawa et al., 2007; Weissman-Fogel et al., 2011). It has also been well documented that negative consequences resulted from maladaptation in the orofacial sensorimotor system can be improved following oral rehabilitation obtained from function restoration measurements (Avivi-Arber et al., 2011). In the present study, after the elimination of the CR–MI discrepancy by stabilization splint, the improvement and rehabilitation of facial-oral environment may facilitate the positive neural plasticity in the frontal and posterior insula cortices. The increased fALFF after treatment may represent a functional recovery in sensory or motor activity. These observations not only indicated that eliminating CR–MI discrepancy may relieve TMD signs and symptoms, but also suggested the effectiveness and psychological mechanisms of the stabilization splint for the treatment of TMD.

Compared with the controls at T2, the lower neural function of the left postcentral gyrus and right superior parietal lobule of the TMD patients (Fig. 2 and Table 5) might be due to decreased sensory inputs from the upper palate which was covered by the stabilization splint for three months, given that both the cortexes are involved in the tactile object discrimination (Stoeckel et al., 2004; Trulsson et al., 2010). This may suggest that functional occlusion should be established by the natural tooth at the appropriate time after stabilization splint treatment to not only control clinical signs and symptoms but also normalize the neural function without creating an intrinsic neural activity reduction in the TMD patients in clinic practice. This potential needs to be debated in future studies.

One limitation of the present study is that the sample size was relatively small. Further studies with larger sample sizes and integrating structural and functional MRI with clinical and cognitive information should be performed to clarify the pathophysiological mechanism of TMD patients with CR–MI discrepancy.

CONCLUSION

In summary, we found decreased regional brain function in the frontal areas related to motor and cognitive function in TMD patients with CR–MI discrepancy. The fALFF in the left precentral gyrus was negatively correlated with vertical CR–MI discrepancy in patients. Altered brain functions in patients recovered after eliminating the CR–MI discrepancy and establishing a stable functional occlusion on CR through the treatment of stabilization splint. These findings may not only provide insight into the cortical neuroplastic processes underlying TMD with CR–MI discrepancy, but also facilitate the understanding of TMD pathogenesis and therapeutic mechanisms of the stabilization splint.

AUTHOR CONTRIBUTIONS

Guarantors of integrity of entire study, S.S. He, F. Li, S.J. Zou, X.Q. Huang, S. Lui, Q.Y. Gong, S. Chen; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, S.S. He, F. Li, F. Song, J.Y. Chen, S. Wu; clinical studies, S.S. He, F. Song, J.Y. Chen, N. He, S. Wu, S.J. Zou, S. Chen; experimental studies, F. Li, X.Q. Huang, S. Lui, Q.Y. Gong; statistical analysis, S.S. He, F. Li., F. Song, J.Y. Chen, S. Wu; and manuscript editing, S.S. He, F. Li, F. Song, S.J. Zou, X.Q. Huang, S. Lui, Q.Y. Gong, S. Chen.

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GLOSSARY

Temporomandibular joint: The temporomandibular joint is the joint of the jaw and is frequently referred to as TMJ. The TMJ is a bilateral synovial articulation between the mandible and temporal bone. The name of the joint is derived from the two bones which form the joint: the upper temporal bone which is part of the cranium (skull), and the lower jawbone or mandible.

Temporomandibular disorders: Temporomandibular disorders (TMD) are defined as a subgroup of craniofacial pain problems that involve the TMJ, masticatory muscles, and associated head and neck musculoskeletal structures. Patients

with temporomandibular disorders most frequently present with pain, limited or asymmetric mandibular motion, and TMJ sounds. The pain or discomfort is often localized to the jaw, TMJ, and muscles of mastication. Common associated symptoms include ear pain and stuffiness, tinnitus, dizziness, neck pain, and headache. In some cases, the onset is acute and symptoms are mild and self-limiting. In other patients, a chronic temporomandibular disorder develops, with persistent pain and physical, behavioral, psychological, and psychosocial symptoms similar to those of patients with chronic pain syndromes in other areas of the body (e.g., arthritis, low back pain, chronic headache, fibromyalgia, and chronic regional pain syndrome), all requiring a coordinated interdisciplinary diagnostic and treatment approach.

Centric relation (CR): The maxillomandibular relationship in which the condyles articulate with the thinnest avascular portion of their respective disks with the condyle in the anterior–superior position against the slopes of the articular eminence. This position is independent of tooth contact.

Maximum intercuspation (MI): The complete intercuspation of the opposing teeth independent of condylar position.

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