Randomized Control Trial

Motor Control Exercise Modulates the Neural Plasticity of the Default Mode Network in Patients with Chronic Low Back Pain

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Background: Motor control exercise (MCE) effectively alleviates nonspecific chronic low back pain (CLBP), but the neural mechanisms underlying this phenomenon are poorly understood.

Objective: To study MCE's neural mechanisms in patients with CLBP by resting-state functional magnetic resonance imaging (rs-fMRI).

Study design: A prospective, single-blind, randomized, controlled trial.

Setting: Department of Rehabilitation Medicine, The First Affiliated Hospital, Sun Yat-sen University.

Methods: 58 patients were randomly assigned to either the MCE or the Manual Therapy (MT) group. Before and after treatment, all the patients underwent ultrasound imaging to measure transversus abdominis (TrA) activation, rs-fMRI scans and questionnaire assessments. We analyzed the activation and connectivity of the bilateral precuneus based on the fractional amplitude of low-frequency fluctuation (fALFF) and effective connectivity (EC) analyses. Further, we determined the association between imaging and clinical measures.

Results: Pain intensity, pain catastrophizing, and pain-related disability were alleviated significantly in both groups post-treatment. However, the MCE group showed a greater reduction in pain-related disability and a better improvement in activation of the right TrA than the MT group. After MCE, patients showed an increase in regional fALFF values in the key node of the default mode network (bilateral precuneus) and decreased EC from the bilateral precuneus to the key node of the frontoparietal network (the left dorsolateral prefrontal cortex (DLPFC)). The pre-to-post-treatment change in the EC from bilateral precuneus into the left DLPFC was significantly correlated with the pre-to-post-treatment change in visual analog scale scores and activation of the right TrA in the MCE group ($r = 0.765$, $P < 0.001$ and $r = 0.481$ and $P = 0.043$ respectively).

Limitations: The present study shows the correlation between the alteration of brain functions and CLBP-related symptoms, which does not reveal the causal effect between them. Further, this study does not estimate the long-term efficacy of MCE on brain function, and the sample size was not calculated based on fMRI data.

Conclusion: These findings demonstrate that MCE may alleviate CLBP symptoms in patients by modifying information transmission from the default mode network to the left frontoparietal network.

Key words: Chronic low back pain, motor control exercise, resting-state functional magnetic resonance imaging, granger causality analysis, precuneus, default mode network, dorsolateral prefrontal cortex, frontoparietal network

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Chronic low back pain (CLBP) poses a great health and economic concern for society. Up to 90% of patients are diagnosed with nonspecific CLBP, where no specific cause for the pain can be identified (1,2). Impairment of the trunk postural control is thought to be the leading cause of this condition, which has been associated with impaired activation of the transversus abdominis (TrA), that can be measured by ultrasound imaging with good test-retest reliability (3-5). TrA activation training has been shown to reduce pain intensity in patients with CLBP (6). Alternately, motor control exercise (MCE) can sufficiently activate core stabilizing muscles, including the TrA, to restore impaired postural control and meet the functional demands of the trunk, thereby alleviating CLBP (5,7,8). A previous study demonstrated that MCE could modulate CLBP patients' motor cortex by employing transcranial magnetic stimulation (TMS) mapping, which was not observed with unskilled walking exercise training (9). However, the study did not correlate motor cortex reorganization with pain intensity ratings. Thus, the underlying neural mechanism of MCE on CLBP is still unknown.

Mounting evidence from structural and resting-state functional magnetic resonance imaging (rs-fMRI) studies suggest that analgesic effects caused by the treatment of CLBP or other chronic pain conditions are associated with neural plasticity in pain-related regions (insula), default mode network (DMN) areas, and the cerebellum (10-13). The DMN, consisting of the medial prefrontal cortex (mPFC), rostral anterior cingulate cortex (rACC), inferior parietal cortex, posterior cingulate cortex and precuneus, is engaged in several neural processes including emotion regulation, memory, and prospection (14). Patients with CLBP demonstrated alterations of the DMN, such as increased activation in the mPFC and decreased resting-state functional connectivity between mPFC/rACC and the frontoparietal network (15,16).

The analgesic effects of exercise, such as resistance and flexibility training, aerobic training, and Tai Chi, among others, were associated with changes in the intrinsic neural activity and resting-state functional connectivity of the DMN in patients with chronic pain disorders (17,18). For instance, submaximal exercise inverses the abnormal activation of the mPFC in myalgic encephalomyelitis (18). Similarly, Tai Chi increases the resting-state functional connectivity between the DMN and frontoparietal network in patients with fibromyalgia and knee osteoarthritis, and this altered connectivity was accompanied by clinical improvements (19,20). Unlike the aforementioned exercises, MCE aims to restore impaired postural control by improving the activation of core stabilizing muscles in patients with CLBP (5,7,8). However, its ability to modulate the DMN's neural plasticity to alleviate CLBP symptoms is still unknown.

This study, therefore, investigated the effects of a 6-week MCE program on the fractional amplitude of low-frequency fluctuation (fALFF) and effective connectivity (EC) in patients with CLBP. We hypothesized that in cases of CLBP, the analgesic effect of MCE is associated with its effects on DMN activation and the connectivity of the DMN to the frontoparietal network.

Methods

Patients

Patients were recruited for this study via advertising (trial registration: ChiCTR2100043113). We only included patients with persistent CLBP for > 3 months or intermittent pain for > 6 months during screening. This study was approved by the Institutional Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Ethics No. [2020]42) and registered at the Chinese Clinical Trial Registry (ChiCTR2100043113). Patients were recruited by a licensed doctor (CJZ) and randomly allocated to the MCE group or manual therapy (MT) group by a statistician (CYF) at a 1:1 ratio according to the computer-generated randomized numbers in a sealed and opaque envelope.

The inclusion criteria for patients with CLBP were as follows: 1) clinical CLBP diagnosis with persistent pain > 3 months or intermittent pain > 6 months; 2) pain score of at least 3 on the Visual Analog Scale (VAS, 0–10) in the previous week; 3) 18–65 years of age; 4) right-hand dominance; 5) absence of neurological and cardio-cerebrovascular diseases, and endocrine disorders; 6) no treatment for back pain in the past 3 months (1-7).

The exclusion criteria were as follows: 1) specific low back pain; 2) a history of cancer or significant unexplained weight loss; 3) current or past history of psychiatric disorders that needed pharmacotherapy; 4) cognitive deficits as defined by a score less than 26 on the Montreal Cognitive Assessment (MoCA) (8), illiteracy or difficulties in communication; 5) routine alcohol or drug dependence, and 6) contraindication for MRI (e.g., claustrophobia, pregnancy, pacemaker, or metal implants in the body) (3).

Sample Size

We calculated the sample size using G*Power statistical software (version 3.1.2; www.gpower.hhu.de) using pain intensity (visual analog scale [VAS] score) as the primary outcome variable (21). Upon accounting for a 40% dropout rate, a minimum of 27 patients in each group were required, assuming an effect size of 0.430 calculated in our previous meta-analysis summarizing MCE for CLBP, an α level of 0.05, and a power (1-beta) of 0.9 (7).

MCE Program

All the patients completed the MCE program under the supervision of a licensed therapist (YLL) with more than 5 years of experience in MCE practice. The MCE program lasted for 6 weeks with 3 sessions of 30 minutes each per week. The details of the MCE are reported in our previous study (8). Patients were not allowed to undergo other treatments or a home exercise program during the treatment period.

MT

A licensed therapist (ZZ) with more than 10 years of experience in MT practice administered muscular relaxation, myofascial release, and mobilization during each session based on physical examination (8). The MT lasted 6 weeks with three sessions of 30 minutes each per week.

Clinical Measures

Questionnaire Assessments

We used VAS to test average pain intensity in the previous week, the 100-point Oswestry Disability Index (ODI) to assess low back pain-related disability, and Pain Catastrophizing Scale (PCS) to assess the extent of patients' catastrophic thinking in response to pain stimuli. All questionnaires have acceptable reliability, with a Cronbach alpha value of 0.78 for the Chinese version of ODI and 0.87 for PCS respectively (22,23).

Ultrasound Measurements

The voluntary activation of bilateral TrA in was measured from images obtained with Sonosite M-Turbo with a linear transducer probe (6–13 MHz, B-mode), following our previously reported method (5). Muscle activation (TrA%) was calculated as percentage change in thickness using the following formula (5):

$$TrA\% = \frac{(Contraction-Rest)}{Rest} \times 100\% \quad (1)$$

MRI Data Acquisition

Structural and functional MRIs were acquired using a 3.0 T MR scanner with a 32–channel head coil (Ingenia; Philips). Patients were instructed to close their eyes, stay awake but motionless, and let their minds wander. High-resolution T1-weighted sagittal images were obtained using a fast field echo pulse sequence with 185 slices, repetition time/echo time (TR/TE) = 7.7 ms/3.5 ms, flip angle (FA) = 8°, acquisition matrix = 2562, field-of-view (FOV) = 256 mm^2 and slice thickness = 1.0 mm. When abnormal signs appeared in the T1-weighted images, T2-FLAIR images were obtained to confirm the presence of brain lesions. Functional MRIs were acquired using the gradient echo-planar imaging sequence as follows: 240 volumes, interleaved scanning, TR/TE = 2000 ms/30 ms, slice thickness = 3.5 mm, intersection gap = 1 mm, acquisition matrix = 64 × 61; FOV = 224 mm^2, FA = 90°, and 33 transverse slices.

Functional Data Processing and Analysis

Processing

Functional images were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) 3.0 Advanced Edition based on Statistical Parametric Mapping (SPM 12) (24). The following steps were involved in preprocessing: 1) removal of the first 10 time points; 2) slicing timing for acquisition time delay correction; 3) realignment for correction of head motion; 4) co-registration of the functional images with the anatomical scan; 5) segmentation of the co-registered anatomical images into white matter, gray matter and cerebrospinal fluid; 6) normalization of images into the Montreal Neurologic Institute (MNI) space; 7) smoothing with a 6-mm FWHM Gaussian kernel; 8) regression analysis to minimize influence on the cerebrospinal fluid, white matter, and head motion (Friston 24 model); and 9) linear detrending and temporal band-pass filtration (0.01–0.1 Hz) (25,26). To correct for head motion, we set the head motion reference standard based on the mean framewise displacement (FD) Jenkinson and excluded patients with motion (mean FD Jenkinson) > 2 × standard deviation (SD) above the group mean motion from analysis after realignment.

fALFF Analysis

fALFF was calculated as the mean of the amplitudes within 0.01–0.10 Hz to reduce the effects of low-frequency drift and high-frequency noise in DPARSF

3.0 Advanced Edition. The calculation process was as follows: 1) using the fast Fourier transform, the time courses of each voxel were converted to the frequency domain to obtain the power spectrum without band-pass filtering; 2) the square root of the power spectrum was calculated at each frequency; 3) fALFF was calculated as the ratio of power spectrum at low frequency (0.01–0.10 Hz) to that of the entire frequency range (0–0.25 Hz, with TR = 2000 ms); 4) the fALFF map was transformed to z-scores for analysis (28).

We conducted statistical analysis of the fALFF maps using SPM 12 in MATLAB2013b (Mathworks). Flexible ANOVA test was performed to analyze the significant time × treatment condition interactions, time, and group effect, which was followed by the paired t-test to examine the changes in fALFF maps within each group. Significance was set at the uncorrected voxel level of $P = 0.005$, followed by the family-wise error (FWE) corrected cluster level of $P = 0.05$ (29).

Seed-to-voxel-based EC

Bivariate coefficient Granger causality analysis (GCA) was conducted to estimate the EC of predefined seeds (X) to the rest of the brain (Y) using the RESTplus software (RESTplus v1.24). The presence of EC from X to Y indicates a causal flow from X to Y, which means that X exerts a "causal influence" on Y by preceding and predicting neuronal activity in Y and vice versa (30). A positive coefficient indicates excitatory influence, and a negative coefficient indicates inhibitory influence (31). The seeds were defined as 6 mm spheres centered on the MNI coordinates of the peak t-value from regions of the altered fALFF maps. The GCA maps were converted to z-scores for analysis. The statistical analysis of the GCA maps was the same as the fALFF analysis.

Statistical Analysis

Statistical analysis was performed with SPSS version 26.0 (SPSS Inc.). We examined each group's normality and homogeneity of continuous variables using the Kolmogorov-Smirnov and Levene's tests, respectively. Continuous variables are presented as means ± standard deviations (SDs), and categorical data is presented as absolute numbers. The Chi-square (Fisher's exact test) was conducted to determine the differences in category variables between groups. The between-group difference among demographics, clinical assessments, and the change from baseline to post-treatment (Δ) clinical measures were analyzed using independent-sample t-tests (Mann-Whitney U tests). We conducted a sensitivity test for the missing data caused by dropouts and technical issues and revealed that the missing data was completely at random (32). Generalized estimating equations (GEEs), followed by Bonferroni corrections, were applied to analyze between- and within-group differences in clinical measures across the covariates time, age and gender. All models included covariates, time effects, treatment effects, and time × treatment interaction effects. Pearson partial correlation analysis was used to assess the correlations between Δclinical measure, ΔfALFF and ΔGCA (with age and gender as confounding covariates) values. Statistical significance was set at $P < 0.05$ for all tests.

Results

Patients

Four hundred and twenty-six patients were screened for eligibility. A total of 58 patients with CLBP were included in this study and were randomized into the MCE (n = 30) or MT group (n = 28). Twenty-nine patients completed the MCE program, with one dropping out because of a traffic accident. Twenty-seven patients completed the MT therapy program, with one dropping out because of pregnancy. The data of 9 patients from the MCE group was excluded from fMRI data analysis, because 3 patients missed the second MRI scan, one patient slept during MRI scan, 2 patients exhibited excessive head motion and 3 patients had incomplete DICOM files. Similarly, the data of 11 patients from the MT group was excluded, because 4 patients missed the second MRI scan, one patient slept during the scan, 3 patients exhibited excessive head motion, 2 patients had incomplete DICOM files due to technical issues, and one had intracranial neoplasm. Finally, the data of 20 patients in the MCE group and 16 patients in the MT group were included in the analysis of fMRI data (Supplemental Fig. S1). The 2 groups included in the intention-to-treat and per-protocol sample did not differ significantly in demographic and clinical characteristics (Table 1 and Supplemental Table S1).

Clinical Assessments in the Per-protocol Sample

Primary Outcome

We observed no significant time × treatment interaction and group effect (B = 0.795, Wald = 3.558, $P = 0.059$ and B = –0.415, Wald = 0.004, $P = 0.951$ respectively), but a significant time effect (B = 3.275, Wald

= 303.686, $P < 0.001$) in VAS scores by GEE. Post-hoc analysis showed that the VAS at post-treatment was significantly lower than at the baseline ($P < 0.001$; Fig. 1). However, no significant difference in ΔVAS between groups was observed ($P = 0.092$; Fig. 1). The analysis of VAS showed similar results in the intention-to-treat-ment sample (Supplemental Fig. S2).

Secondary Outcome

A significant time × treatment interaction was observed in the ODI scores by GEE (B = 5.248, Wald = 4.296, $P = 0.022$). Post-hoc analysis demonstrated that both groups showed significantly lower ODI scores at post-treatment (all $P < 0.001$), but the MCE group showed significantly lower ODI scores and greater ΔODI compared to the MT group at post-treatment ($P = 0.005$ and 0.037 respectively; Fig. 1 and Supplemental Fig. S2).

We observed no significant time × treatment interaction and group effect (B = 1.037, Wald = 1.179, $P = 0.672$ and B = -3.075, Wald = 2.027, $P = 0.155$ respectively), but a significant time effect (B = 8.813, Wald = 57.898, $P < 0.001$) in PCS scores by GEE. Post-hoc analysis showed that the post-treatment PCS scores were significantly lower than the baseline value ($P < 0.001$; Fig. 1).

A significant time × treatment interaction was observed in the right TrA% by GEE (B = –0.316, Wald

Table 1. *Characteristics of patients included in analysis of fMRI data (per-protocol sample).*

Variable	MCE (n = 20)	MT (n = 16)	*P* value
Age (years)	29.300 ± 8.633	28.500 ± 5.033	0.373
Gender, male/female, n †	7/13	6/10	0.877
Education length (years)	17.000 ± 2.384	18.375 ± 2.446	0.290
BMI (kg/m^2)	21.338 ± 2.426	21.802 ± 2.608	0.479
Duration of CLBP (months)	44.850 ± 39.933	37.500 ± 48.922	0.352
MoCA	28.650 ± 0.933	29.125 ± 0.500	0.211
HAMD	7.950 ± 4.548	5.875 ± 4.349	0.077
VAS (0–10 cm)	5.775 ±1.293	5.400 ± 0.098	0.479
ODI (0-100) (%)	15.417 ± 6.947	15.784 ± 7.806	0.863
PCS (0-52)	11.400 ± 6.692	13.375 ± 9.625	0.473
lTrA%	58.814± 25.143	47.600 ± 28.541	0.123
rTrA%	46.644 ± 19.068	59.247 ± 28.600	0.365

Abbreviations: BMI, Body Mass Index; MCE, motor control exercise; MoCA, Montreal Cognitive Assessment; MT, manual therapy; HAMD, Hamilton Depression Scale; lTrA%, left transversus abdominis percent thickness change; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; rTrA%, right transversus abdominis percent thickness change; VAS, Visual Analog Scale. The data was represented as mean ± standard deviation unless otherwise indicated. † Chi-square.

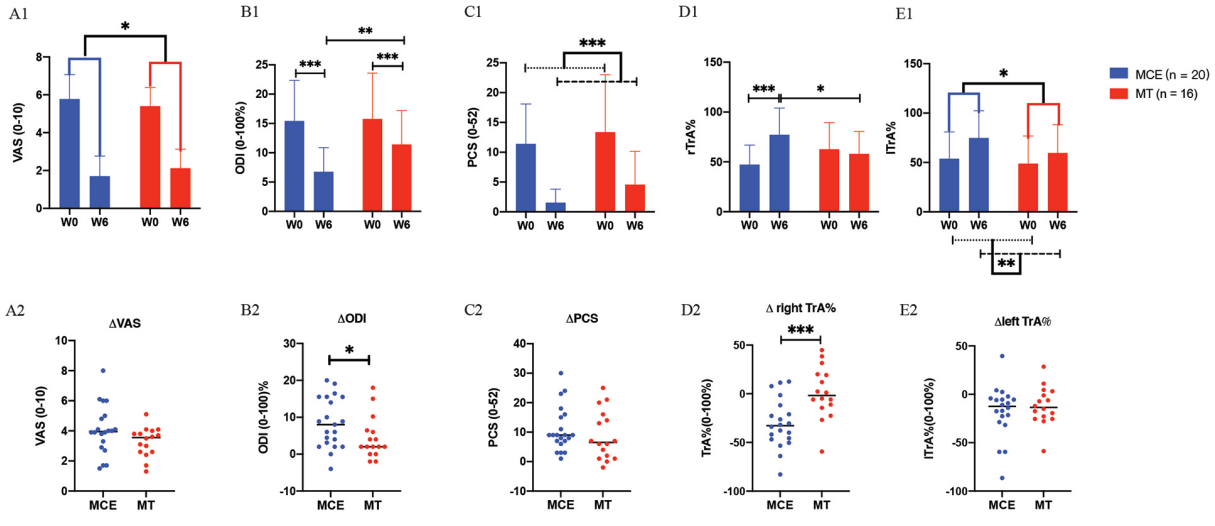

Fig. 1. *Results of clinical assessments in the per-protocol sample.*
Abbreviations: MCE, motor control exercise; MT, manual therapy; lTrA%, left transversus abdominis percent thickness change; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; rTrA%, right transversus abdominis percent thickness change; VAS, Visual Analogue Scale. Δ = change from baseline to post-treatment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

= 14.078, $P < 0.001$). Post-hoc analysis demonstrated that only the MCE group showed significant improvement post-treatment in the right TrA% ($P < 0.001$; Fig. 1 and Supplemental Fig. S2). Post-treatment, both the right TrA% and the ∆right TrA% were greater in the MCE group than in the MT group ($P = 0.013$ and 0.001 respectively; Fig. 1).

We observed no significant time × treatment interaction and group effect (B = –0.058, Wald = 0.592, $P = 0.442$ and B = 0.139, Wald = 1.989, $P = 0.158$ respectively), but a significant time effect (B = –0.120, Wald = 15.489, $P < 0.001$) in the left TrA% by GEE. Post-hoc analysis showed that the post-treatment left TrA% was significantly greater than the baseline ($P = 0.002$ and 0.012 respectively; Fig. 1). However, the ∆left TrA% was comparable between the 2 groups ($p = 0.475$; Fig. 1).

The analysis of the secondary outcomes showed similar results in the intention-to-treatment sample (Supplemental Fig. S2).

Increased fALFF Values in Bilateral Precuneus after 6 Weeks of MCE

No significant time × treatment condition interactions, time or group effects were observed through the fALFF values (2-tailed, voxel level uncorrected $P < 0.005$, cluster level FWE corrected $P < 0.05$). Only the MCE group exhibited increased post-treatment fALFF values in the bilateral precuneus within the global gray mask (2-tailed, voxel level uncorrected $P < 0.005$, cluster level FWE corrected $P < 0.05$; Fig. 2). Table 2 represents the differences between the baseline and post-treatment fALFF maps within the MCE group. No significant clusters which demonstrated changes in values across time were found in the MT group within the global gray mask.

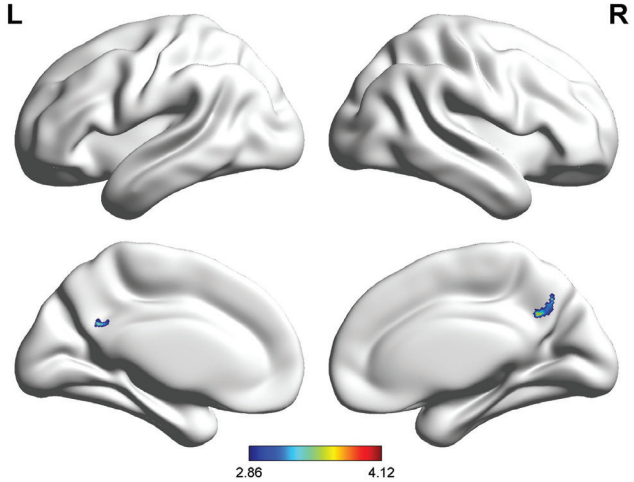

Fig. 2. *The difference in fALFF values between baseline and post-treatment in the MCE group (2-tailed, voxel level uncorrected $P < 0.005$, cluster level FWE corrected $P < 0.05$).*
Abbreviations: MCE, motor control exercise; fALFF, fractional amplitude of low-frequency fluctuation; FWE, family-wise error.

Decreased EC from Bilateral Precuneus into the Left Rostral Middle Frontal Gyrus after 6 Weeks of MCE

The GCA demonstrated no significant time × treatment condition interactions, time, or group effect (2-tailed, voxel level uncorrected $P < 0.005$, cluster level FWE corrected $P < 0.05$). Patients exhibited significantly decreased EC from the bilateral precuneus to the left rostral middle frontal gyrus (part of the dorsolateral prefrontal cortex [DLPFC]) within the global gray mask after MCE (2-tailed, voxel level uncorrected $P < 0.005$, cluster level FWE corrected $P < 0.05$; Table 3 and Fig. 3). No significant clusters demonstrating changes in EC across time were found within the global gray mask in the MT group, using the bilateral precuneus as a seed.

Association Between Functional Data and Clinical Assessments

The partial correlation analyses showed a significant association between ∆EC from the bilateral precuneus into the DLPFC, ∆VAS and ∆right TrA% (r = 0.765, $P < 0.001$ and r = 0.481, $P = 0.043$ respectively; Fig. 4) in the MCE group.

Discussion

In this study, we aimed to identify the brain mechanisms supporting the clinical applications of MCE in CLBP treatment using rs-fMRI. After the 6-week treatment, only the MCE group showed significantly reduced disability, increased right TrA and bilateral precuneus activation, and decreased inhibitory causal flow from the bilateral precuneus

Table 2. *The area of significantly increased fALFF values post MCE program.*

Brain area	MNI coordinates			t value	Cluster size (voxels)
	x	y	z		
Bilateral precuneus	9	-54	33	4.1002	97

Abbreviations: fALFF: fractional amplitude of low-frequency fluctuation; HC, healthy controls; MCE: motor control exercise; MNI: Montreal Neurologic Institute. * Number of voxels.

Table 3. *Reduced effective connectivity post MCE program in GCA.*

Causal inflow from bilateral precuneus to the rest of the brain					
Brain area	Peak MNI coordinates (x, y, z)	Mean (SD) Path Coefficient		t values (peak)	Cluster size (voxels)
		Pre-MCE	Post-MCE		
DLPFC.L	-45, 45, 15	-0.118 (1.256)	-0.351 (1.513)	-5.3736	83

Abbreviations: DLPFC.L, left dorsolateral prefrontal cortex; GCA: granger causal analysis; MCE: motor control exercise; MNI: Montreal Neurologic Institute.

into the left DLPFC. Furthermore, the pre-to-post-treatment change in inhibitory causal flow from the bilateral precuneus into the left DLPFC was positively correlated with pre-to-post-treatment changes in pain intensity and right TrA activation in the MCE group.

Although patients in both groups felt less pain post-treatment, only those in the MCE group showed significantly increased activation in the bilateral precuneus, shown by larger fALFF values after treatment. The precuneus, the core hub of the DMN, is crucial for attention, memory, and self-referential processes (33). It plays an essential role in retrieving episodic memory and motor imagery (34). Its activity was reduced in patients with chronic orofacial neuropathic pain, in healthy controls during tonic pain stimuli, and in CLBP patients after pain-exacerbating maneuvers (33,35). The depressed activity of the precuneus in pain states implies that pain competes with other attention-demanding stimuli for cognitive resources (33,36).

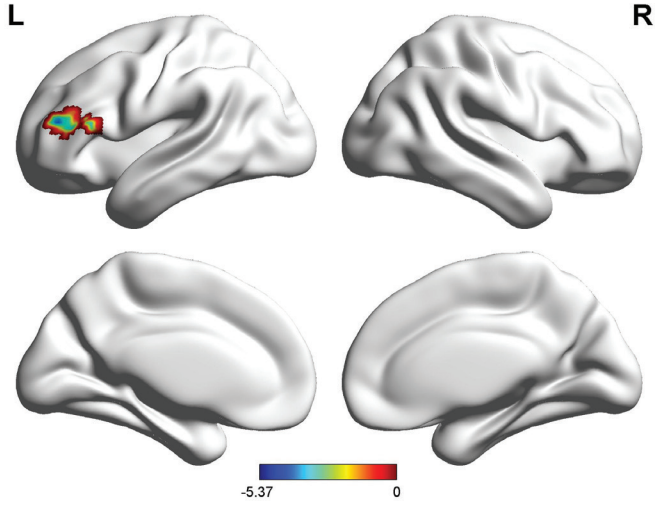

Fig. 3. *The EC from the bilateral precuneus to the left dorsal prefrontal cortex were significantly decreased in patients with CLBP after MCE treatment.*
Abbreviations: CLBP, chronic low back pain; EC, effective connectivity; MCE, motor control exercise.

MCE is an attention-demanding task, and the patients' need to focus on the external task and memorize the series of movements may compete with pain for cognitive resources. Furthermore, the MCE program used in this study was individualized and progressively administered by gradually increasing each set's exercise time and difficulty level; thus, patients had to constantly learn and retrieve the memory of movements, which could result in increased precuneus activity. On the contrary, patients in the MT group did not undergo any attention-demanding tasks during the therapy program; therefore, the activity in their precuneus remained unaltered. Previous studies found increased activity in the posterior DMN (posterior cingulate gyrus, right precuneus, right middle frontal gyrus, and right inferior frontal gyrus) after spinal manipulative therapy (37,38). This discrepancy may have been due to the use of different thresholds for the multiple comparison corrections, as we used a stricter method to avoid false positives (FWE), instead of the Monte Carlo simulations used in previous studies (37-40).

Additionally, the relatively small sample size in our MT group might also account for the discrepancy. Previous research has shown that exercises such as endurance running can improve the white matter's microstructural integrity and increase activity in the bilateral precuneus (41-44). Our observation of heightened activity in the precuneus after the MCE program provides further evidence for the effect of physical exercise on neural plasticity in patients with chronic pain disorders.

In this study, we observed a significant decrease in inhibitory causal flow from bilateral precuneus into the left DLPFC, which is positively correlated with pain intensity. DLPFC is a key node of the frontoparietal network, thought to play a pivotal role in nociceptive processing and pain modulation (45). According to a recent review and meta-analysis, physical exercise training mainly impacts functional activity in the precuneus

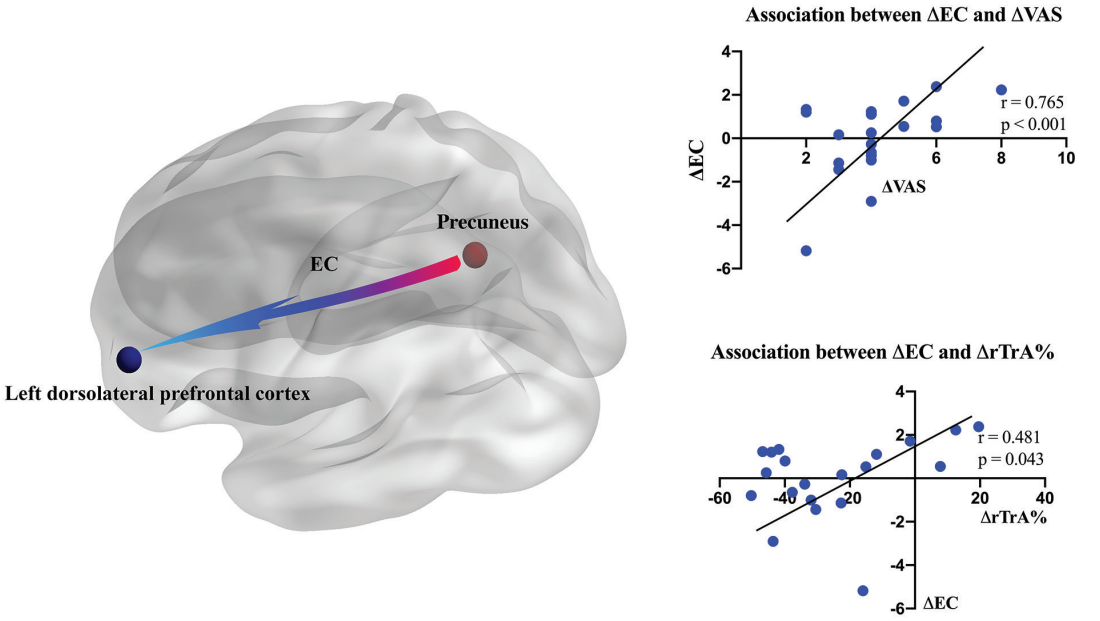

Fig. 4. *The ΔEC from bilateral precuneus to the left DLPFC was significantly correlated with the Δ rTrA% and the ΔVAS after MCE.*
Abbreviations: EC, effective connectivity; lTrA%, left transversus abdominis percent thickness change; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; rTrA%, right transversus abdominis percent thickness change; SFMPQ, short form of the McGill Pain; and VAS, Visual Analog Scale. Δ = change from baseline to post-treatment.

and the association between the DMN and frontoparietal network (especially the DLPFC), which is consistent with our observations (17,42,43). Moreover, increasing the left DLPFC activity by high frequency repetitive transcranial magnetic stimulation (rTMS) induces an analgesic effect both in chronic pain and in response to provoked pain (46). The activation of the left DLPFC under pressure stimuli was significantly increased in patients with fibromyalgia and healthy controls following a 15-week resistance exercise program performed biweekly under supervision (47). Based on these results, we inferred that decreased inhibitory causal flow from the bilateral precuneus into the left DLPFC following MCE could heighten left DLPFC activation in response to provoked pain in patients with CLBP. However, this requires task fMRI studies to verify.

Furthermore, we found that the pre-to-post MCE change in the EC from the bilateral precuneus into the left DLPFC was significantly associated with the pre-to-post-MCE change in right TrA activation. Our previous studies have demonstrated that the left DLPFC is activated during the postural control task in patients with CLBP, and that increasing the activity of the left DLPFC by intermittent theta burst stimulation over the left DLPFC might improve the right TrA activation pattern during the postural control task (48,49). Our results further support the idea that DLPFC, especially the left side, plays an important role in pain management and postural control in patients with CLBP. Thus, future studies might verify that non-invasive brain stimulations that target the functioning of the left DLPFC are a promising treatment option for CLBP patients.

Limitations

It is important to note that this study explored the correlation between alterations in activation and connectivity of the posterior DMN node (the bilateral precuneus) and CLBP-related symptoms. Future investigation is needed to explore the causal effect between MCE-related neural plasticity and CLBP symptoms. Furthermore, the sample size was calculated based on the primary outcome (VAS scores) but not based on image data, which might reduce the power of the time × group interaction effect on the fMRI data analysis. Additionally, as we did not conduct follow-up assessments, the long-term treatment effects of MCE on the activation

and effective connectivity of the DMN cannot be determined. Future studies to investigate the long-term benefits of MCE on CLBP are necessary.

Conclusion

Our findings demonstrated that MCE induces pain alleviation, activates the key node of the DMN, and diminishes the inhibitory causal flow from the DMN into the left frontoparietal network. Furthermore, the altered interaction between the key node of the DMN and the frontoparietal network is positively associated with pain alleviation and improved TrA activation after MCE. Our results provide preliminary evidence that MCE-induced CLBP alleviation could be related to the modulation of causal flow from the DMN into the left frontoparietal network. This evidence for MCE-induced neural mechanisms may support its clinical application in CLBP treatment.

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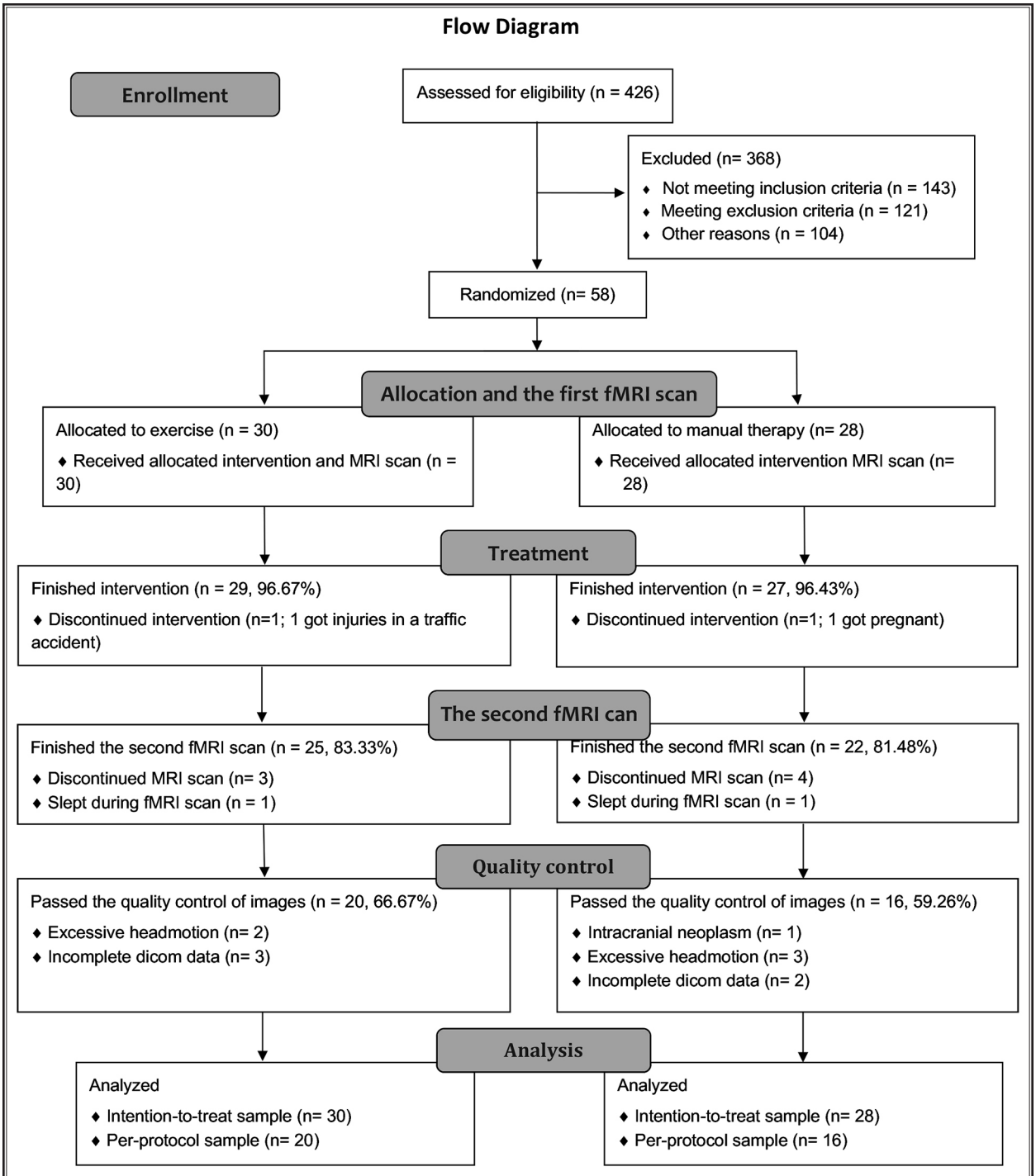
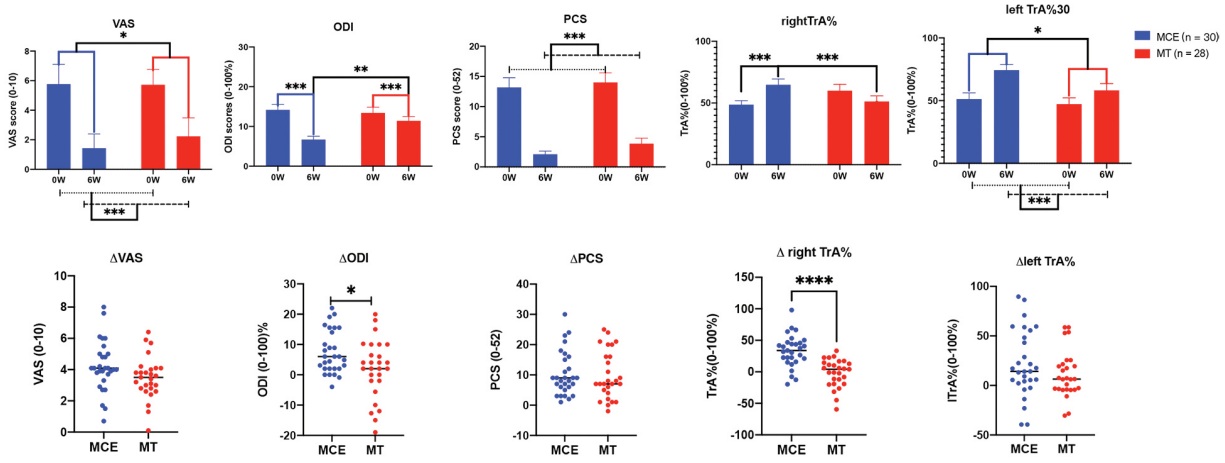
Supplemental Table S1. ***Demographic and clinical characteristics in the intention-to-treat sample.***

Variable	**MCE (n = 30)**	**MT (n = 28)**	***P* value**
Age (years)	28.172 ±7.654	29.259 ± 6.224	0.373
Gender, male/female, n †	20/10	10/18	0.683
Education length (years)	17.172 ± 2.054	18.148 ± 2.332	0.654
BMI (Kg/m^2)	20.796 ± 2.702	22.241 ± 4.135	0.144
Duration of CLBP (months)	38.034 ± 36.244	34.037 ± 43.416	0.616
MoCA	28.621 ± 0.775	28.556 ± 0.698	0.515
HAMD	3.207 ± 2.226	2.667 ± 1.881	0.360
VAS (0–10 cm)	5.772 ±1.361	5.704 ±1.049	0.834
ODI (0-100) (%)	14.386 ± 7.741	13.318 ± 7.656	0.606
SFMPQ (0-45)	8.426 ± 4.249	10.250 ± 6.424	0.387
PCS (0-52)	12.483 ± 8.223	13.704 ± 8.448	0.586
lTrA%	52.573 ± 26.609	46.867 ± 26.547	0.569
rTrA%	47.944 ± 17.603	60.269 ± 28.838	0.063

Abbreviations: BMI: body mass index; CLBP: chronic low back pain; HAMD: Hamilton Depression Scale; lTrA%: left transversus abdominis percent thickness change; MCE: motor control exercise; MoCA, Montreal Cognitive Assessment; MT: manual therapy; ODI: Oswestry Disability Index; PCS: Pain Catastrophizing Scale; rTrA%: right transversus abdominis percent thickness change; SFMPQ: Short-Form McGill pain questionnaire; VAS: Visual Analog Scale. The data was represented as mean ± SD unless otherwise indicated. † Chi-square.



Supplemental Fig. S1. *Trial flowchart*.



Supplemental Fig. S2. *Results of clinical assessments for MCE group or MT group in the per-protocol sample. (A) Differences in VAS scores. (B) Differences in ODI scores. (C) Differences in PCS scores. (D) Differences in left TrA%. (I) Differences in the right TrA%.*

Abbreviations: MCE, motor control exercise; MT, manual therapy; lTrA%, left transversus abdominis percent thickness change; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; rTrA%, right transversus abdominis percent thickness change; VAS, Visual Analog Scale. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.001$.

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