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ORIGINAL ARTICLE

Analgesic efficacy of transcranial combined peripheral magnetic stimulation in chronic nonspecific low back pain: a fNIRS study

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ABSTRACT

BACKGROUND: Magnetic stimulation has a potential therapeutic effect on patients with chronic nonspecific low back pain (CNLBP). However, the efficacy and underlying brain mechanisms of closed-loop magnetic stimulation for CNLBP remain unclear.
AIM: This study aims to investigate the analgesic efficacy and brain activation of repetitive transcranial magnetic stimulation (rTMS) combined with repetitive peripheral magnetic stimulation (rPMS) in patients with CNLBP.
DESIGN: This was a single-center, double-blind, randomized controlled trial.
SETTING: Huashan Hospital.
POPULATION: CNLBP.
METHODS: Thirty patients with CNLBP were randomly allocated into the experimental group and control group, with fifteen patients in each group. Patients in both groups received CNLBP-related health education. On this basis, patients in the experimental group received a two-week rTMS combined with rPMS treatment, while the control group received rPMS treatment combined with sham-rTMS stimulation. Visual analogue scale (VAS), Oswestry Disability Index (ODI), and Neurometer CPT sensory nerve quantitative detector were used to evaluate the participants before and after treatment. In addition, functional near-infrared imaging (fNIRS) was employed to ascertain participants' brain function.
RESULTS: After treatment, both groups exhibited a significant decrease in VAS and ODI scores compared to their pre-treatment levels (all $P<0.05$). While there was no statistical significance between the two groups. Neurometer CPT revealed that the experimental group improved the pain threshold of C-fiber on the unaffected side ($P=0.036$). In addition, compared with the control group, the experimental group exhibited a notable increase in the activation of the somatosensory association cortex (SAC) region and an improvement in the functional connectivity of brain regions, including SAC and the primary motor cortex (PMC), after treatment.
CONCLUSIONS: Combining rTMS with rPMS can significantly relieve pain and remodel brain regions in individuals with CNLBP. This closed-loop rehabilitation model paradigm merits additional clinical investigation and implementation.
CLINICAL REHABILITATION IMPACT: Magnetic stimulation therapy based on closed-loop rehabilitation mode has a good prospect for clinical rehabilitation for patients with CNLBP.

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KEY WORDS: Low back pain; Near-infrared spectroscopy; Rehabilitation.

Chronic nonspecific low back pain (CNLBP) is a prevalent chronic syndrome characterized by persistent pain or severe discomfort arising in the lower back that lasts for more than three months without any pathological abnormality.[1] CNLBP is one of the most common health issues worldwide, with a growing prevalence each year,

particularly among younger individuals.[2] According to a systematic review of 165 studies conducted in 54 countries, CNLBP has a point prevalence of 11.9±2.0%, with the highest prevalence among females and individuals aged between 40 and 80 years.[3] In addition, the GBD 2021 Low Back Pain Collaborators have indicated that there will be approximately 843 million (with a range of 759-933 million) cases of prevalent low back pain (LBP) cases by 2050.[4] Besides imposing a severe impact on individuals' quality of life, CNLBP has also resulted in substantial economic and social burdens.[5]

Currently, there is a lack of specific evidence-based clinical practice recommendations for treating CNLBP due to the unidentified pathoanatomical cause.[6] Individuals with CNLBP are often advised to use primary interventions, including nonsteroidal anti-inflammatory drugs, antidepressants, psychosocial treatments, and complementary and alternative medicine (CAM).[7] Although pharmacological interventions such as opioids and muscarinic medications offer substantial pain relief, they come with adverse effects, including drowsiness, dizziness, and nausea, rendering them unsuitable for long-term treatments.[8] Therefore, there is a paramount need to explore non-pharmacological treatments for CNLBP. Structural and functional alternations in the brain have attracted attention recently because they could possibly serve as biomarkers linking anatomical changes to pain perception.[9] Studies have identified potential disease-specific modifications in both white and grey matter regions of the brain in CNLBP patients, suggesting that chronic pain is associated with structural reorganization.[10] Consequently, the application of stimuli to the brain that could reorganize its connections might hold promise as a potential therapeutic avenue for CNLBP.[11]

Magnetic stimulation is a therapeutic modality utilizing pulsed magnetic fields of a certain intensity to stimulate nerves and muscles, aiming to achieve therapeutic goals. This method can be categorized into repetitive transcranial magnetic stimulation (rTMS) and repetitive peripheral magnetic stimulation (rPMS) based on the site of stimulation.[12] Due to their non-invasive, safe, effective, and user-friendly characteristics, both rTMS and rPMS have found extensive application in chronic pain rehabilitation.[13, 14] A meta-analysis of randomized controlled trials indicated that rPMS can effectively reduce pain intensity and enhance functional capacity in individuals with LBP.[15] Based on closed-loop theory, central interventions coupled with peripheral interventions have demonstrated superior efficacy in improving rehabilitation outcomes.[16] However, whether the closed-loop model of rTMS combined with rPMS is more effective than rPMS alone in alleviating pain symptoms in patients with CNLBP remains unknown. In addition, there exists a research gap regarding magnetic stimulation-induced alternations in brain function among CNLBP individuals.

To address the aforementioned concerns, this study aims to conduct a preliminary investigation into the effectiveness of combining rTMS with rPMS for treating individuals with CNLBP. In addition, we investigate the potential changes in brain function by using functional near-infrared spectroscopy (fNIRS).

Materials and methods

Study design

In this double-blind, two-group, randomized controlled trial, patients with CNLBP were allocated to receive either rTMS combined with rPMS or sham rTMS combined with rPMS. The study protocol was approved by the Ethics Committee of Huashan Hospital, Fudan University (No. KY2022-511) and registered with the Chinese Clinical Trial Registry (ChiCTR2200061399).

Participants

CNLBP patients in this study were consecutively recruited from the outpatient physiatry/physiotherapy clinic at Huashan Hospital, Fudan University, between December 2022 and August 2023, subsequent to providing informed consent. Inclusion criteria comprised: diagnosed of unilateral CNLBP;[17] ages between 20 to 65 years; body mass index (BMI) within the normal range ($18.5 \leq BMI \leq 25$); visual analogue scale (VAS) score ≥ 3; and right-handedness. Exclusion criteria included: history of spinal fractures, spinal dislocations, spinal cord injury, inflammatory arthritides, neoplasms, or malignancies; significant primary diseases affecting liver, heart, lung, kidney, or blood system; mental disorders; pregnancy, lactation, or presence of dysmenorrhea.

Sample size

Sample size determination was conducted using PASS software (NCSS Statistical Software). According to the results of previous relevant studies,[15, 18] the difference (2 points) and standard deviation (3.0) of the primary outcome, which was VAS, were used as a reference for the sample size calculation. Based on this effect size, a sample size of 24 was deemed necessary with a two-sided significance level of 0.05% and 80% power to detect the differ-

ence between the experimental and the control group. Accounting for potential dropouts of up to 20%, a total of 30 subjects (15 in each group) were enrolled to meet sample size estimation criteria.

Randomization, allocation, and blinding

Upon obtaining informed consent, eligible participants were randomly assigned to either the experimental group (rTMS combined with rPMS) or control group (sham rTMS combined with rPMS) in a 1:1 allocation. The allocation concealment process was rigorously blinded and executed sequentially according to the recruitment order. This process utilized a computer-generated random allocation schedule operated by a senior statistician affiliated with the Centre for Biostatistics, Design, Measurement, and Evaluation (CBDME) of Huashan Hospital, Fudan University. Notification of group assignment for each participant was conveyed to patients, research coordinators, and physiotherapists via a sealed opaque envelope. While researchers responsible for data collection and analysis were blinded, physiotherapists were not.

Experimental procedures

Intervention equipment: The YRD-CCY-IA magnetic stimulation equipment (Yiruide Co., Wuhan, China) was utilized for the intervention. The resting motor threshold (RMT) was determined experimentally as the lowest stimulation intensity eliciting motor evoked potentials (MEP) ≥50 mV in 50% of trials. In addition, the cortical latency of the subjects was recorded.

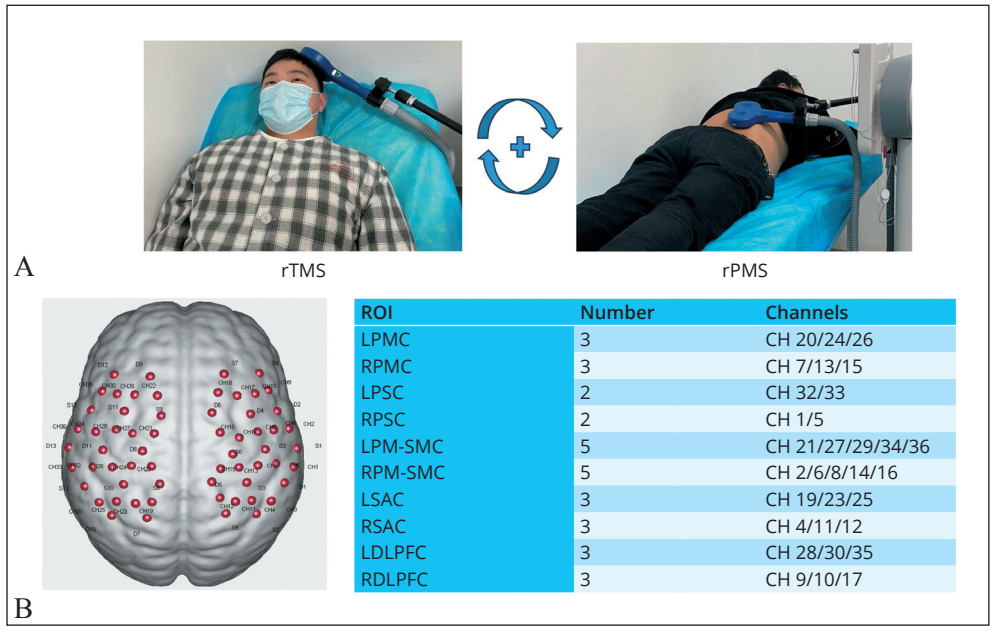
- rTMS: stimulation targeted the primary motor cortex (M1) contralateral to the pain side, employing a stimulation frequency of 20 Hz, a stimulation intensity of 90% RMT, and delivery of 1200 pulses.[19, 20]
- rPMS: stimulation was applied to the low back pain point at a frequency of 20 Hz, with stimulation intensity set at 35-40% of the maximum output intensity of the instrument. The protocol entailed a total of 4000 pulses administered with slight lumbar extension as the standard.[21]

Patients in both groups received routine physiotherapy and education, with the experimental group receiving rTMS combined with rPMS treatment, while the control group receiving sham rTMS (using a placebo coil) combined with rPMS treatment. Referring to relevant literature,[12] we used closed-loop treatment by applying rTMS first and then immediately following it with rPMS. Treatment sessions were conducted once a day, five times a week, over a two-week period (Figure 1A).

Outcome measures

The primary outcome: The primary outcome measure was pain intensity quantified via Visual Analogue Scale (VAS) score.[22]

The secondary outcome: The Oswestry disability index (ODI)[23] scale was used to assess the severity of the lumbar disorder, while the EuroQol-5 Dimension (EQ-5D) scale[24]



ROI	Number	Channels
LPMC	3	CH 20/24/26
RPMC	3	CH 7/13/15
LPSC	2	CH 32/33
RPSC	2	CH 1/5
LPM-SMC	5	CH 21/27/29/34/36
RPM-SMC	5	CH 2/6/8/14/16
LSAC	3	CH 19/23/25
RSAC	3	CH 4/11/12
LDLPFC	3	CH 28/30/35
RDLPFC	3	CH 9/10/17

Figure 1.—Experimental procedure and distribution map of fNIRS channels. A) The M1 was located by the MEP module of the TMS instrument, and then 1200 pulses rTMS plus 4000 pulses rPMS were performed. B) fNIRS 36 channels distribution map and regions of interest map.
PMC: primary motor cortex; PSC: primary somatosensory cortex; PM–SMC: pre-motor and supplementary motor cortex; SAC: somatosensory association cortex; DLPFC: the dorsolateral prefrontal cortex.

evaluated patients' health status and quality of life. Additionally, the Neurometer CPT sensory nerve quantitative detector was utilized to evaluate the quantitative sensory threshold (Current perception threshold, CPT) and pain threshold (pain tolerance threshold, PTT) of the sensory nerve.[25]

The NirScan fNIRS system (Danyang Huichuang Medical Equipment Co. Ltd, China) measured hemoglobin concentrations during the task and resting state of pre-and post-treatment.

Analysis of fNIRS data

Data of fNIRS were processed with NirSpark software (Danyang Huichuang Medical Equipment Co., Ltd., China) and Matlab2014a software (The Mathworks, Natick, MA, USA). To prepare the patient's data for analysis, the original file was converted into a compatible format, followed by a preprocessing step. Specifically, fNIRS data from patients with the right-side lesion were mirrored to align with the corresponding fNIRS channels on the opposite side, with the affected hemisphere reference as the left side. This adjustment facilitated the analysis of lesion locations across all subjects. Subsequently, the general linear model (GLM) was employed to model the data, estimate parameters, and derive β value. These values served as the basis for extracting relevant experimental effects and establishing contrast vectors. The 36 channels were categorized into five regions of interest (ROI) in the left and right brain, namely the primary motor cortex (PMC), primary somatosensory cortex (PSC), pre-motor and supplementary motor cortex (PM–SMC), somatosensory association cortex (SAC), and dorsolateral prefrontal cortex (DLPFC) (Figure 1B). Furthermore, to evaluate brain functional connectivity, resting-state data were analyzed using seed point correlation analysis, whole-brain correlation analysis, and independent component analysis.

Statistical analysis

Statistical analysis was conducted using Stata, version 14.1 (StataCorp). Data normality was confirmed with the Shapiro-Wilk Test. Two-tailed *t*-tests (continuous variables) and the Chi-square test (categorical variables) were utilized to compare baseline measures between the two groups. Baseline characteristics of both groups are presented as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Independent samples were compared by two-sample *t*-test, and matched-paired samples were compared by paired *t*-test. Correlations between the difference in VAS and the difference in activation of RPM-SMC and LDLPFC score were analyzed using Pearson's r correlation analyses. All statistical tests were two-tailed with a significance level of 0.05.

Data availability statement

The data associated with the paper are available in the Chengqi He repository.

Results

Participant characteristics

The flow chart for participants is presented in Figure 2. A total of 98 patients from Huashan Hospital were evaluated

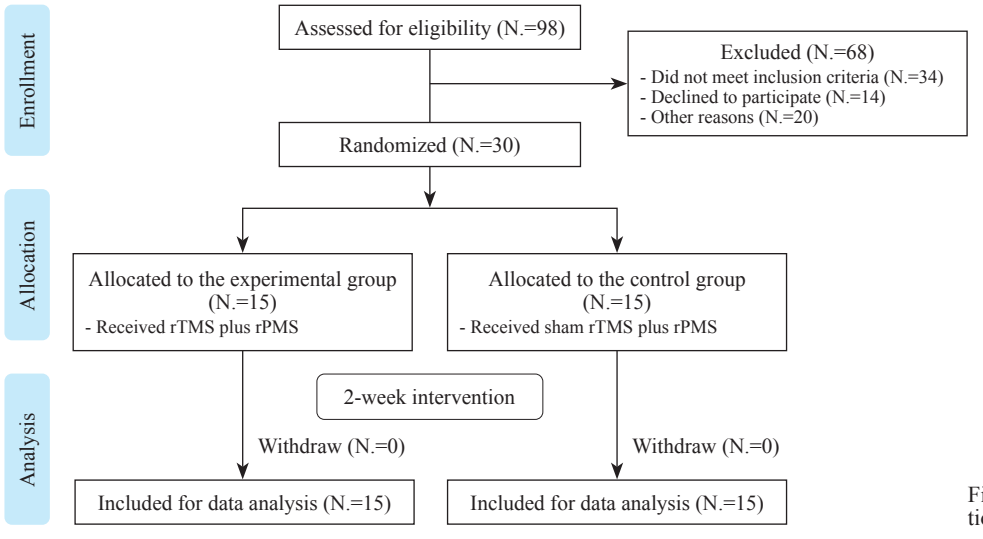


Figure 2.—Flow chart for subject selection and assignment.

TABLE I.—*Demographics for two groups.*

Parameter	Experimental group	Control group
N.	15	15
Sex		
Men	3	5
Women	12	10
Age (years)	46.21±9.18	50.13±12.72
BMI (kg/m²)	22.91±2.49	23.47±3.07
Duration of pain (months)	7.57±5.50	7.13±5.51

for eligibility, with 30 CNLBP patients ultimately included in the study. The participants' demographic characteristics are shown in Table I. No significant differences were observed between the groups regarding gender, age, BMI, or duration of pain. In addition, there were no significant differences between the two groups in primary outcome, secondary outcome, and fNIRS datas at baseline.

The primary outcome

Results for the primary outcome measures are presented in Table II. Comparative analysis revealed a significant decrease in VAS in both groups post-treatment compared to pre-treatment levels (experiment group: P=0.006; control group: P=0.006). However, there was no statistically significant difference in VAS score between the groups after intervention (P=0.064).

The secondary outcome

Post-treatment ODI and EQ-5D scores exhibited significant improvement in both groups compared to pre-treatment values (ODI: experiment group: P=0.005, control group: P=0.008; EQ-5D: experiment group: P=0.026, control group: P=0.010). Additionally, the CPT5Hz score of the unaffected side in the experimental group demonstrated a significant decrease post-treatment compared to pre-treatment levels. However, no significant between-group differences were observed for the pre-test and post-test ODI and EQ-5D values. Furthermore, there were no significant differences in other CPT and PTT points (Table II).

Brain activation

Intra-group comparison within the experimental group showed significant activation in channel 6 (RPM-SMC, P=0.014) and channel 28 (LDLPFC, P=0.03) post-treatment compared to pre-treatment (Figure 3A). In contrast, no significant activation was observed within the control group before and after treatment (all P>0.05, Figure 3B). Comparison between the groups indicated significant activation in channel 19 (LSAC, P=0.011) post-treatment in the experimental group compared to the control group (Figure 3C).

Functional connectivity changes

Resting-state brain functional connectivity results are presented in Figure 3D. The intra-group analysis demonstrated significant activation of ROIs in both the experimental and the control group post-treatment. Comparison of the brain functional connection intensity post-treatment between the groups revealed that the experimental group exhibited significantly enhanced internal functional connection in-

TABLE II.—*Comparison of outcomes in two groups.*

Outcomes	Experimental group		Control group	
	Pre-test	Post-test	Pre-test	Post-test
VAS (score)	5.83±1.93	2.04±1.45 [a]	5.03±1.73	2.14±1.419 [b]
ODI (%)	17.58±7.79	8.48±7.29 [a]	20.22±6.49	8.89±9.13 [b]
EQ-5D (score)	0.86±0.06	0.94±0.06 [a]	0.85±0.06	0.95±0.07 [b]
Affected CPT 2k Hz (score)	126.18±43.36	150.55±35.61	143.18±57.10	170.82±54.06
Affected CPT 250 Hz (score)	31.20±16.83	36.73±13.81	32.77±13.95	44.45±20.58
Affected CPT 5 Hz (score)	17.65±13.82	19.18±13.77	21.46±11.56	28.24±18.62
Unaffected CPT 2k Hz (score)	153.82±57.73	162.45±54.51	168.18±58.11	191.55±73.51
Unaffected CPT 250 Hz (score)	47.00±24.64	39.64±14.15	44.73±18.30	53.45±30.67
Unaffected CPT 5 Hz (score)	35.65±13.97	23.08±13.41 [a]	29.75±20.11	32.37±29.29
Affected PTT 2k Hz (score)	15.18±4.23	13.55±4.20	15.27±4.58	15.18±2.48
Affected PTT 250 Hz (score)	9.18±4.46	7.91±2.84	9.00±4.19	9.18±2.56
Affected PTT 5 Hz (score)	15.18±6.96	12.82±6.11	14.09±6.07	13.09±5.01
Unaffected PTT 2K Hz (score)	16.00±3.89	13.27±5.14	15.27±3.03	14.64±3.04
Unaffected PTT 250 Hz (score)	9.97±5.11	7.55±2.81	8.18±2.92	8.36±2.29
Unaffected PTT 5 Hz (score)	14.82±6.88	12.91±5.31	15.00±4.56	13.09±5.82
MEP-latency	24.81±3.34	23.40±2.72	23.95±1.66	23.05±0.35

[a] <0.05: Comparison pre- and post-test in experimental group; [b] <0.05: comparison pre- and post-test in control group.

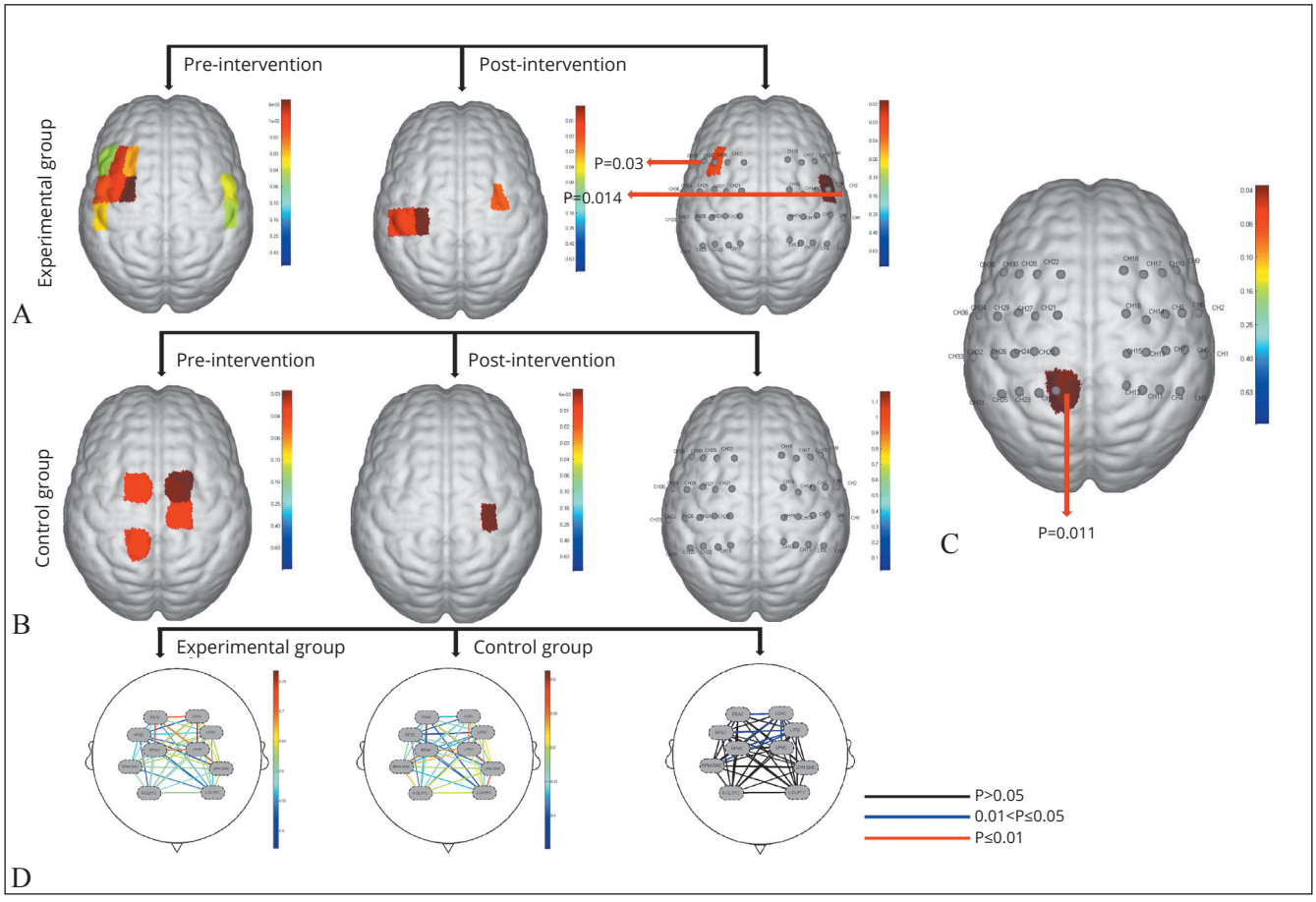


Figure 3.—The brain activation and functional connection matrix of the experimental group and the control group before and after treatment. A) Changes in brain function activation in the experimental group before and after treatment. B) Changes in brain function activation in the control group before and after treatment. C) Comparison of brain function activation after treatment between two groups. D) Comparison of brain functional connectivity changes after treatment between the two groups.

tensity of LPSC and LSAC compared to the control group. Additionally, the experimental group showed significant strengthening of functional connections between RPSC-LPSC, LPSC-RPMC, LPSC-RPM-SMC, LPSC-LSAC, RPMC-LSAC, and RSAC-LSAC (all P<0.05, Table III).

Brain and pain intensity correlations

Correlation analysis between VAS scores and fNIRS brain function revealed that the difference in VAS scores within the experimental group did not exhibit a positive correlation with the functional connectivity of RPM-SMC and LDPPFC (Figure 4).

Safety

No significant adverse events occurred during the clinical trial. Reported adverse events included mild headaches experienced by two participants in the experimental group, which persisted after the initial stimulation. These headaches had been anticipated and communicated to the patients prior to the commencement of rTMS. Furthermore,

TABLE III.—*Comparison of functional connection strength of ROIs between the two groups after intervention.*

ROI	Groups		T value	P value
	Experimental group	Control group		
LPSC-LPSC	0.84±0.10	0.59±0.29	2.22	0.044
LSAC-LSAC	0.78±0.09	0.52±0.26	3.14	0.007
RPSC-LPSC	0.56±0.15	0.35±0.24	2.32	0.031
LPSC-RPMC	0.63±0.14	0.42±0.26	2.26	0.035
LPSC-RPM-SMC	0.58±0.14	0.42±0.19	2.18	0.041
LPSC-LSAC	0.66±0.13	0.46±0.21	2.52	0.021
RPMC-LSAC	0.66±0.13	0.43±0.27	2.42	0.028
RSAC-LSAC	0.69±0.13	0.42±0.31	2.66	0.018

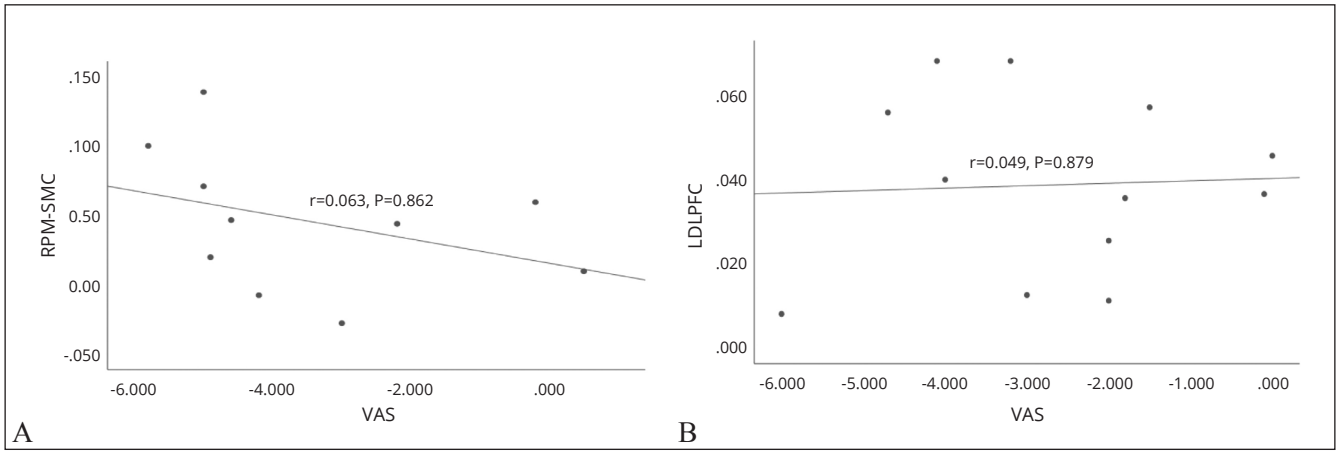


Figure 4.—Correlation analysis between the difference in VAS and the difference in activation of RPM-SMC (A) and LDLPFC (B) before and after treatment within the experimental group.

the headaches were promptly alleviated with appropriate medical care.

Discussion

This study represents the first RCT investigating the analgesic efficacy and brain activity of rTMS combined with rPMS for individuals with CNLBP. Encouraging results were observed in both the rTMS plus rPMS group and the sham rTMS plus rPMS group in terms of pain relief and functional improvement. Analysis of brain function revealed significant activation in LSAC within the experimental group post-treatment compared to the control group. Furthermore, resting-state functional connectivity analysis demonstrated a significant enhancement in functional connectivity within ROIs in the experimental group compared to the control group.

The intervention of rTMS combined with rPMS exhibited potential analgesic and therapeutic effects for patients with CNLBP. Given the limited efficacy and substantial risks associated with surgery and pharmacological interventions, there is a pressing need for conservative non-pharmacological interventions in patients with CNLBP.[26-28] Previous studies indicated that rPMS holds promise as a modality for managing acute and chronic pain.[13, 29] Since 2011, Lo's team has conducted investigations into the efficacy of a single session of rPMS for lumbosacral spondylosis.[30] Subsequently, various research teams have sequentially explored the effectiveness of rPMS with different parameters for addressing low back pain. A meta-analysis of RCTs has indicated that one session to four weeks of rPMS showed significant efficacy in terms of reducing pain intensity and improving functional disability.[15] In addition, rTMS targeting the contralateral primary motor cortex has been shown to notably alleviate neuropathic pain.[31] In 2016, Rene's group found that one week of rTMS could significantly relieve pain in LBP patients. In the field of neuroscience, it has been observed that integrating central regulation with peripheral therapy can lead to improved rehabilitation prognosis of patients.[32-34] In this study, the closed-loop rehabilitation mode involves the combination of rTMS with rPMS to manage patients with CNLBP. We found that two weeks of this combination therapy significantly resulted in significant improvement in pain symptoms and quality of life in patients with CNLBP. However, there was no significant difference in pain relief compared to rPMS alone. This may be due to the short intervention period, which might not allow sufficient time for rTMS to exert its effects on central pain modulation.[12] Additionally, the complexity of pain mechanisms means that the immediate benefits of rPMS could overshadow those of the combined therapy.[15] Individual variability in patient response and potential measurement limitations may also contribute to these findings. Further studies with longer treatment durations and broader outcome measures are needed to assess the true effectiveness of the combined approach.[35]

Moreover, rTMS combined with rPMS was found to enhance C fiber sensitivity on the unaffected side of the lumbar region in patients with CNLBP. NeurometerCPT is a selective quantitative sensory nerve detector that determines the conduction threshold of the sensory nerve by measuring the electrosensory threshold of the skin and mucosa.[36] The function of Different sensory fibers can be

evaluated with different frequencies of current: 2000 Hz for Aβ-fiber, 250 Hz for Aδ-fiber, and 5 Hz for C-fiber, respectively.[37] It was revealed that rTMS combined with rPMS treatment could significantly downregulate the PPT-5Hz threshold in the unaffected lumbar region. C-fiber is a kind of unmyelinated sensory nerve fiber with a small diameter. As the main nerve fiber to conduct chronic persistent pain, C-fiber is highly sensitive to thermal, mechanical and chemical stimulations.[38] Results here suggest that magnetic stimulation could modulate the sensory threshold of patients. Specifically, rTMS, in combination with rPMS, potentially alleviates pain symptoms by improving the pain threshold of C-fiber on the patient's healthy side.

Furthermore, rTMS was shown to significantly activate the SAC region of the contralateral brain and enhance the functional connectivity of ROIs in CNLBP patients. Previous studies have demonstrated that CNLBP leads to anatomical changes in the dorsolateral prefrontal lobe, temporal lobe, and primary somatosensory cortex, indicating-that chronic pain associated with structural reorganization.[6] Notably, our fNIRS data analysis revealed that rTMS combined with rPMS had a substantial positive effect on the excitability of the affected SAC region and the functional connectivity of bilateral PSC, PMC, and PM-SAC brain regions, outperforming rPMS alone. Research indicated that the PSC region plays a vital role in the regulation of postural control, and the reorganization of the motor cortex network can potentially improve the effectiveness of feedforward postural control.[39] We hypothesize that rTMS can directly influence the PSC region, contributing to the reorganization of brain function in patients. This finding highlights the potential of rTMS as a therapeutic tool for reshaping brain activity patterns in chronic pain conditions. Such insights are valuable for future research, suggesting that targeting specific brain regions with rTMS could enhance treatment strategies and improve outcomes for patients with CNLBP.

Clinical implications and future directions

The current study underscores the potential of rTMS combined with rPMS as a potential treatment for CNLBP patients. Further research is warranted from the following aspects. First of all, future studies should explore longer-term interventions and follow-up further to determine the effect of this combination therapy. Secondly, the therapeutic effect of rTMS combined with rPMS in other brain regions, such as the dorsolateral prefrontal lobe and PSC area, needs further exploration. Thirdly, the determination of optimal treatment parameters of rTMS and rPMS in CNLBP patients is also imperative. Finally, the exploration of various brain region detection methods to assess changes in brain function is essential for advancing our understanding of CNLBP treatment modalities.

Limitation of the study

This study has several limitations. Firstly, there was no follow-up observation of patients beyond the study period. In addition, the absence of a neuronavigational system capable of targeting the primary motor cortex based on the functional imaging examination represents a limitation of this study.

Conclusions

In summary, the findings of this study suggested that two-week rTMS combined with rPMS or rPMS alone could effectively reduce pain intensity in CNLBP patients. Moreover, rTMS combined with rPMS significantly activates SAC and enhances functional connectivity of sensorimotor brain areas compared with rPMS alone. This closed-loop rehabilitation model warrants further investigation and clinical application.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Chengqi He contributed to the conception of the study. Chong Li performed the data analyses and wrote the manuscript. Jing Hu revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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