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Impact of Intermittent Theta Burst Stimulation on Pain Relief and Brain Connectivity in Chronic Low Back Pain

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Keywords: chronic low back pain | DLPFC | functional connectivity | iTBS

ABSTRACT

Background: This randomised clinical trial investigated the effect of intermittent theta burst stimulation (iTBS) over the dorsolateral prefrontal cortex (DLPFC) on pain alleviation in patients with chronic low back pain (CLBP) and its underlying mechanisms.

Methods: Forty CLBP patients were randomly assigned to receive either active or sham iTBS combined with core stability exercise. Pain assessments were completed before and after the intervention. Eleven patients from each group underwent resting-state functional magnetic resonance imaging scans pre- and post-intervention to analyse DLPFC activation and connectivity with other brain regions.

Results: The active iTBS group had a greater pain reduction than the sham group ($p = 0.05$, 95% CI: −0.009 to 1.109). In the active and sham groups, 80% (16/20) and 40% (8/20) reached the minimal clinically important difference, respectively, with a number needed to treat of 2.5. For the Fear-Avoidance Beliefs Questionnaire, there was a significant difference between the two groups ($p = 0.011$, $r = 0.40$). The active iTBS group showed a significantly enhanced functional connectivity between the left DLPFC and the right cerebellum, as well as both occipital gyri (voxel-level, $p < 0.001$; cluster-level familywise error rate, $p < 0.01$). Spearman's correlation analysis showed a significant negative correlation between Numerical Rating Scale and the FC of the left DLPFC and the right cerebellum (rho = −0.55, $p = 0.008$), the right (rho = −0.439, $p = 0.01$), and left occipital gyri (rho = −0.45, $p = 0.034$).

Conclusion: iTBS may alleviate pain in CLBP patients by enhancing DLPFC connectivity with the cerebellum and occipital gyrus.

Significance: This study showed a facilitatory effect of iTBS on alleviating CLBP, which might be modulated by brain functional connectivity.

Trial Registration

Chinese Clinical Trial Registry: ChiCTR2200064899

Jiajia Yang, Xiaoyu Gao and Xue Cheng are contributed equally to this work and share first authorship.

1 | Introduction

Chronic low back pain (CLBP) is a widespread health issue with a substantial socioeconomic impact on patients and caregivers (Spencer L James et al. 2018). CLBP can be caused by disc degeneration, inflammation, and persistent muscle tension due to poor posture (Maher et al. 2017). However, targeting these issues with medications and exercise may cause side effects and have limited long-term effects (Chou et al. 2017; Urits et al. 2019). Recent research has indicated that patients with CLBP exhibit changes in neuroplasticity that are significantly associated with chronic pain (Kregel et al. 2015), suggesting neural modulation in the pain network of the brain as a potential treatment for CLBP.

Functional magnetic resonance imaging (fMRI) shows that CLBP patients have structural and functional changes in the prefrontal cortex, cingulate gyrus, insula, thalamus, cerebellum, and periaqueductal grey (Apkarian et al. 2004; Kregel et al. 2015; Yuan et al. 2017). The dorsolateral prefrontal cortex (DLPFC) is essential for cognitive functions and pain inhibition (Ong et al. 2019), as well as pain sensory integration, influencing pain awareness and avoidance (Ihara et al. 2019). During chronic pain, the DLPFC shows reduced volume, altered activation, and decreased connectivity with other brain regions (Seminowicz and Moayedi 2017). Our previous study found increased DLPFC activation in CLBP patients (Zeng et al. 2023). Additionally, decreased functional connectivity between the DLPFC and insula correlates with pain severity in CLBP (Ceko et al. 2015), and CLBP is linked to reduced prefrontal and thalamic grey matter density (Apkarian et al. 2004). This set of evidence suggests the importance of the DLPFC in the pain-related brain network and its potential as a target for pain treatment. Exercise intervention may primarily activate the motor network (Yu et al. 2021), which may explain its poor long-term efficacy. Non-invasive neuromodulation of the DLPFC may represent a more effective treatment option.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that modulates brain activity (Klomjai et al. 2015). Studies suggest rTMS may benefit CLBP, but more rigorous trials are needed (Olechowski et al. 2023). A meta-analysis found high-frequency rTMS over the DLPFC has analgesic effects and improves the emotional aspects of pain in migraines (Zhou et al. 2024). Intermittent theta burst stimulation (iTBS), a newer rTMS mode, may outperform conventional rTMS in treating chronic pain with stronger and longer-lasting effects on cortical excitability (Ambriz-Tututi et al. 2016; Cardenas-Morales et al. 2010; Huang et al. 2005; Yang et al. 2023). iTBS reportedly reduces chronic pain symptoms, including in patients with facial pain and migraines (Kohútová et al. 2017; Kothari et al. 2022; Sahu et al. 2019). Another recent study found that iTBS over the DLPFC decreased chronic pain in patients with depression (Kirupaharan et al. 2024). iTBS of the DLPFC may therefore have significant potential in alleviating chronic pain. However, its effects and potential mechanism remain unclear in CLBP patients.

In this study, iTBS of the DLPFC was combined with core stability exercise (CSE) to treat patients with CLBP. We hypothesise that iTBS may reduce pain by modulating DLPFC functional connectivity.

2 | Methods

2.1 | Participants

The sample size was determined using GPower software version 3.1 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). A previous study conducted by Freigang et al. reported that the effect size of the reduction in pain intensity after the intervention was 0.52 (Freigang et al. 2021). Based on a significance level of 0.05, a power of 80%, and a dropout rate of 20%, 20 participants were required in each group.

Participants were recruited between March 2022 and January 2023 via a social media platform and advertisements displayed at the clinic. The inclusion criteria were as follows: (1) clinically diagnosed CLBP, with intermittent or persistent pain below the 12th rib of the lower back for at least 12 weeks; (2) aged between 18 and 40 years; (3) Numerical Rating Scale (NRS) ≥ 3 points; (4) right-handed; (5) absence of neurological diseases such as stroke, sciatica due to peripheral nerve damage, or Parkinson's disease; (6) no drug treatment for low back pain in the past 3 months; and (7) eligible for transcranial magnetic stimulation (TMS). The exclusion criteria were as follows: (1) presence of spinal stenosis, spondylolisthesis, vertebral fracture, osteoporosis, tumour, tuberculosis, severe or progressive scoliosis, or low back pain due to rheumatic immune/inflammatory disease; (2) dysmenorrhea or postpartum or pregnancy-related low back pain; (3) history of back surgery in the past 2 years, or back or shoulder injury in the past year; (4) presence of severe cardiovascular or cerebrovascular diseases or high blood pressure; (5) presence of cancer or unexplained weight loss; (6) depression and anxiety disorder, as determined by the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale; (7) cognitive dysfunction, illiteracy, or difficulty communicating; and (8) other contraindications to TMS, including metal implants, previous seizures, or use of anticonvulsants, or other conditions incompatible with this study.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University and registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2200064899). Written informed consent was obtained from all participants before treatment initiation. The study was conducted in accordance with the Code of Ethics of the World Medical Association, as outlined in the Declaration of Helsinki.

2.2 | Study Design

The flow chart of this double-blind, sham-controlled study is presented in Figure 1. The physiotherapists (R.C.F. and H.X.) who conducted the intervention were not blinded to the group allocation, but the participants, the researcher collecting the outcome data (J.J.Y.), and the researcher analysing the outcome data (X.C.) were blinded. Patients with CLBP who met

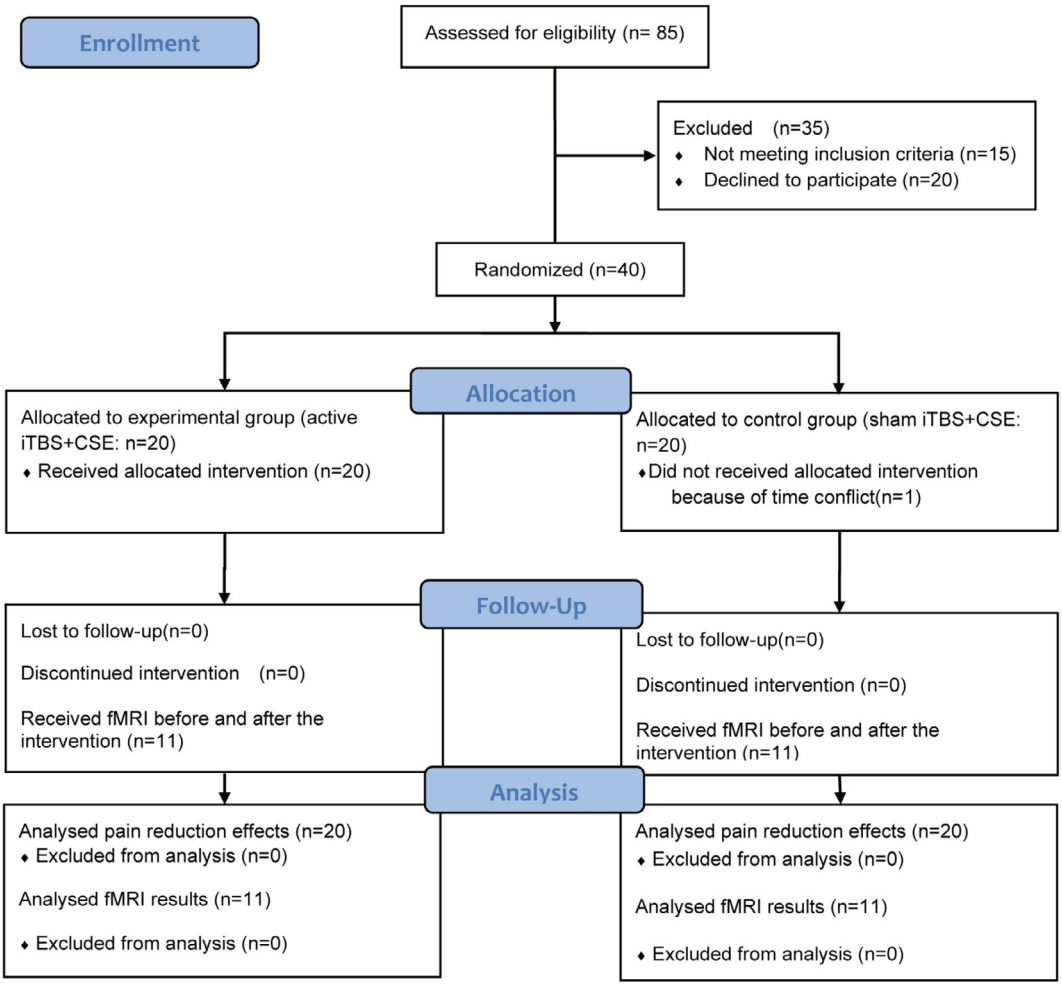

FIGURE 1 | CONSORT flow diagram of the study. CSE, core stability exercise; fMRI, functional magnetic resonance imaging; iTBS, intermittent theta burst stimulation.

the eligibility criteria were randomised into either the active stimulation or sham groups. At the end of the experiment, the participants in both groups reported that they were not aware of the group identity. The active stimulation group received iTBS in combination with CSEs, whereas the sham group received sham iTBS in combination with CSEs. All experimental procedures were conducted at the Department of Rehabilitation Medicine, First Affiliated Hospital of Sun Yat-sen University between March 2022 and January 2023.

2.3 | Randomisation

Randomisation was performed using computer-generated numbers. Participants were assigned according to the randomisation sequence by a research assistant (Z.W.L.) who was not otherwise involved in the study.

2.4 | Experimental Procedures

Demographic information including name, sex, height, weight, and educational level was collected from participants, who were then randomly assigned to a group and underwent the appropriate 4-week intervention. Adverse events were recorded throughout the study period. The primary outcome of pain intensity and the secondary outcomes of disability, fear-avoidance beliefs of all the participants were evaluated before and after the 4-week intervention period. Only 11 participants in each group underwent fMRI before and after the intervention due to the social distancing policy during the coronavirus disease 2019 (COVID-19) pandemic. The study protocol is illustrated in Figure 1.

2.5 | Interventions

2.5.1 | Intermittent Theta Burst Stimulation

iTBS was performed using an NS5000 Magnetic Stimulator (Wuhan Yiruide Medical Equipment New Technology Co. Ltd., Wuhan, China). Participants underwent a total of 16 sessions of iTBS over the left DLPFC, with four sessions per week for 4 weeks. iTBS was delivered 10 min prior to CSE. The iTBS protocol for a single session began with a triplet 50 Hz burst, repeated at 5 Hz, 2 s on and 8 s off; 600 pulses were delivered within 200 s in each session (Huang et al. 2005). The recording electrode of the TMS-integrated electromyograph was placed on the first dorsal interosseous muscle of the right hand, with the reference electrode positioned on a nearby bony prominence. The TMS coil was moved over in the left M1

region to locate the area where the largest motor-evoked potentials (MEPs) could be consistently elicited. The resting motor threshold (RMT) for the participant was defined as the minimum stimulation intensity required to elicit at least five MEPs with amplitudes $\geq 50\,\mu V$ in 10 consecutive single-pulse stimulations. The stimulation intensity was 80% of the RMT (Grossheinrich et al. 2009). During active stimulation, a 7-cm outer-diameter figure-of-eight TMS coil was positioned at the DLPFC. The coil was placed closely tangential to the surface of the scalp. The scalp location of the left DLPFC was defined as the position of the F3 electrode of the electroencephalogram cap, designed according to the International 10–20 system (Herwig et al. 2003). For sham stimulation, the coil was tilted at a 90° angle from the original stimulation position relative to the scalp surface (Takano et al. 2021). All treatments were performed with the coil positioned in a posterior–anterior direction, parallel to the midline.

2.5.2 | Core Stability Exercise

In accordance with our previous study (Wang et al. 2023), all participants underwent a 4-week exercise training program with four sessions per week. Each training session lasted for 40 min and was supervised by two professional physiotherapists (R.C.F. and H.X.). In the first 2 weeks, the participants learned how to activate deep trunk muscles (such as the transverse abdominis and multifidus) and reduce overactivity in superficial muscles during movements such as cat-cow, bird dog, double-leg bridge, and single-leg bridge. In the final 2 weeks, the participants performed a series of functional movements aimed at enhancing trunk stability during trunk and limb movements. Each movement during the training session was maintained for 20 s and repeated six to eight times, with a break of approximately 10 s between every two repetitions.

2.6 | Study Outcomes

2.6.1 | Primary Outcome

Pain intensity, as the primary outcome, was assessed using an 11-point NRS ranging from 0 (no pain) to 10 (worst pain imaginable) (Nugent et al. 2021). The minimal clinically important difference (MCID), determined as "the smallest change that is important to patients" (van der Roer et al. 2006), has been defined for pain intensity as an improvement of more than three points on the NRS (Ostelo et al. 2008). We also calculated the "substantial" improvement rate, defined as a reduction in pain of approximately 50% or more (Dworkin et al. 2008). The Number Needed to Treat (NNT) represents the number of patients who need to be treated with a particular intervention to achieve one additional beneficial outcome. It quantifies the effectiveness of a treatment by indicating how many patients must be treated to obtain a specific benefit. A low NNT value is to be preferred: a small number of patients need to be treated in order to achieve an additional treatment success. Mathematically, the NNT is calculated as the reciprocal of the absolute risk reduction (ARR), where ARR represents the difference in MCID achievement rates between the active and sham groups (Dekker et al. 2024).

$$\text{NNT} = \frac{1}{\text{active group MCID} - \text{sham group MCID}}$$

2.6.2 | Secondary Outcomes

The Roland–Morris Disability Questionnaire (RMDQ) was used to assess functional disabilities. It comprises 24 items related to difficulties completing activities of daily living. Each item agreed with adds to the score, with the final score ranging from 0 (no difficulty) to 24 (severe difficulty). The MCID for the RMDQ has been defined as a 30% reduction from the baseline (Jordan et al. 2006). The NNT was also calculated to quantify the difference between the two groups in the result of RMDQ.

The Fear-Avoidance Beliefs Questionnaire (FABQ) was used to measure fear-avoidance beliefs. Participants rated their agreement with each of the 16 items on a 7-point Likert scale ranging from 0 (completely disagree) to 6 (completely agree). Higher total scores indicate stronger fear-avoidance beliefs. The MCID for the FABQ has been defined as a reduction of more than 13 points from the baseline (George et al. 2006). The NNT was also calculated to quantify the difference between the two groups in the result of FABQ.

2.6.3 | fMRI Acquisition and Analysis

Resting-state fMRI was performed using a 3.0-Tesla Magnetom Prisma MRI scanner (Siemens Healthineers, Erlangen, Germany) with the following sequence parameters: slices = 37, repetition time = 2000 ms, echo time = 30 ms, fractional anisotropy = 90, acquisition matrix = 64 × 64, field-of-view = 224 × 224 mm, thickness = 3.5 mm and gap = 0 mm. During fMRI, all participants were asked to remain awake, keep their eyes closed, relax, and refrain from thinking.

Resting-state fMRI data were preprocessed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK) and the RESTplus toolbox based on MATLAB version 2013b (MathWorks Inc., Natick, MA, USA) (Jia et al. 2019). The preprocessing steps were as follows: (1) the first 10 time points were removed to establish magnetic field stability; (2) a slice-timing correction was applied to account for volume acquisition delays during slicing; (3) realignment was performed to correct for motion across different time points; (4) head motion parameters were computed by estimating the translation in each direction and the rotational angles along each axis for each volume; (5) for normalisation, individual structural images were registered to the mean functional image and subsequently, the transformed structural image was segmented and normalised to the Montreal Neurological Institute space using diffeomorphic anatomical registration through the exponentiated Lie algebra technique and resampled to 3-mm cubic voxels (Ashburner 2007; Lancaster et al. 2007); (6) spatial smoothing was performed using a 6-mm full-width at half-maximum Gaussian kernel; (7) several nuisance covariates were regressed from the data, including linear drift, motion parameters estimated using the Friston-24 model, white matter signals, and cerebrospinal fluid signals; and (8) images were filtered with a frequency window of 0.01–0.08 Hz.

After preprocessing, seed-based functional connectivity analysis was conducted using the RESTplus toolbox. Using the Automated Anatomical Labelling atlas, the left and right DLPFC

were selected as regions of interest for further analysis (Tzourio-Mazoyer et al. 2002). Functional connectivity measures were computed between the seed region of interest and every other voxel in the brain. The DLPFC was selected as the seed region. The residual BOLD time course was extracted from a given seed and its first-level correlation maps were estimated by computing the Pearson's correlation coefficients between the extracted time course and the time courses of all other voxels in the brain. Correlation coefficients were transformed into Fisher's Z-scores to increase normality and improve the second-level general linear model analysis. The DLPFC seed-to-voxel functional connectivity was estimated for each participant.

Fractional amplitude of Low-frequency fluctuations (fALFFs) and regional homogeneity (ReHo) were used to measure the spontaneous local activity of individual regions or voxels. For the amplitude of Low-frequency fluctuations (ALFFs), a fast Fourier transform was used to transform the time series for each voxel to the frequency domain to obtain the power spectrum, and the square root of the power spectrum was calculated and averaged across 0.01–0.08 Hz. The fALFF was computed as the ratio of the power spectrum of a given frequency range to the entire frequency range, which significantly improved the sensitivity and specificity of regional spontaneous brain activity detection. ReHo was used to assess local temporal synchronisation by calculating Kendall's coefficient of concordance between the time series of a given voxel and its 26 nearest neighbours. RESTPlus was used to extract the fALFF and ReHo values of the left and right DLPFC for statistical analysis.

2.7 | Statistical Analysis

We conducted an intention-to-treat analysis in this study. Multiple imputation was used where values were missing (Austin et al. 2021). Statistical analyses were performed using IBM SPSS Statistics for Windows software version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to check the distribution of continuous variables before and after the intervention. Normally distributed NRS and RMDQ data were compared using a two-way repeated-measures analysis of variance, with a within-subject factor of time and a between-subject factor of group. Pairwise comparisons at the main effect level were conducted if there was an interaction between time and group. Statistical significance was set at $p < 0.05$. Non-normally distributed FABQ data were compared using the Mann–Whitney U test to assess changes from baseline to post-treatment (Δ). Independent samples t tests with family-wise error rate (FWE) corrections were employed to analyse between-group differences in fMRI outcomes before and after the intervention. For DLPFC seed-to-voxel functional connectivity, cluster-wise FWE correction $p < 0.01$ indicated statistical significance. For fALFF and ReHo, an FWE correction $p < 0.025$ indicated statistical significance. Spearman's correlation analysis was used to assess the correlation between changes in functional connectivity and changes in NRS, RMDQ, and FABQ scores after the intervention.

3 | Results

3.1 | Baseline Characteristics

A total of 40 participants met the eligibility criteria and were included in the study. One participant in the sham group withdrew from the study because of scheduling conflicts. The demographic characteristics of the two groups of participants are summarised in Table 1.

3.2 | Primary Outcome

The results of the mixed-effects model showed that the NRS score timing was significant, suggesting that both the sham and active groups showed significant improvements in pain after the intervention ($F = 253$, $p < 0.001$, $\eta^2p = 0.87$). The time × group interaction effect was also significant ($F = 8.3$, $p = 0.006$, $\eta^2p = 0.18$). Post hoc analysis showed that the experimental group experienced a

TABLE 1 | Demographic characteristics of the two groups of participants.

	Active group ($n = 20$)	Sham group ($n = 20$)		
Characteristic	**Mean ± SD**	**Mean ± SD**	***t* or χ^2**	***p***
Sex (male/female)	8/12	9/11	0.10[a]	0.75
Age (years)	29.53 ± 5.35	27.20 ± 3.75	−1.84	0.07
Height (cm)	164.48 ± 5.05	167.10 ± 6.58	1.49	0.15
Weight (kg)	59.05 ± 7.83	62.95 ± 9.91	1.36	0.18
Pain duration (years)	3.84 ± 2.55	3.00 ± 2.86	−0.89	0.38
Education (years)	18.53 ± 2.86	18.05 ± 1.70	−0.47	0.64
Baseline scores				
NRS	5.75 ± 1.71	5.15 ± 1.35	−1.23	0.23
RMDQ	7.55 ± 6.03	6.10 ± 4.36	−0.87	0.39
FABQ	54.55 ± 12.92	49.85 ± 9.57	−1.31	0.20

Abbreviations: FABQ, Fear-Avoidance Beliefs Questionnaire; NRS, Numerical Rating Scale; RMDQ, Roland-Morris Disability Questionnaire; SD, standard deviation.
[a]χ^2 value.

greater decrease in NRS scores than the control group ($p = 0.05$, 95% CI: −0.009 to 1.109). In the active group, 20 out of 20 patients (100%) achieved at least 50% pain relief compared to their baseline levels, whereas in the sham group, the proportion was 11 out of 20 patients (55%). The NRS MCID was met by 16 out of 20 participants (80%) in the active group and 8 out of 20 participants (40%) in the sham group (Table 2 and Figure 2). The calculated NNT was 2.5, indicating that for every approximately three patients treated with the active intervention, one patient would achieve the NRS MCID.

3.3 | Secondary Outcomes

The effect of time on RMDQ scores was significant ($F = 52.46$, $p < 0.05$, $\eta^2p = 0.58$). However, the group and time × group interaction effect was not significant ($F = 0.14$, $p = 0.71$, $\eta^2p = 0.71$). The RMDQ MCID was met by 15 out of 20 participants (75%) in the active group and 17 out of 20 participants (85%) in the sham group (Table 2 and Figure 2). The calculated NNT was 10, indicating that for every approximately 10 patients treated with the active intervention, one patient would achieve the RMDQ MCID.

TABLE 2 | Clinical scores before and after the intervention.

	Active group ($n = 20$)	Sham group ($n = 20$)	Main effect (time)			Main effect (group)			Time × group interact effect		
	mean ± SD	mean ± SD	*F*	*p*	η^2p	*F*	*p*	η^2p	*F*	*p*	η^2p
NRS											
Before	5.75 ± 1.71	5.15 ± 1.35	253	< 0.001*	0.87	0.00	0.94	0.00	8.3	< 0.01*	0.18
After	2 ± 0.92	2.55 ± 0.83									
RMDQ											
Before	7.55 ± 6.03	6.85 ± 5.31	52.46	< 0.001*	0.58	0.95	0.34	0.03	0.14	0.71	0.00
After	3.5 ± 3.89	2.42 ± 2.22									

Abbreviations: NRS, Numerical Rating Scale; RMDQ, Roland-Morris Disability Questionnaire; SD, standard deviation.
*$p < 0.05$.

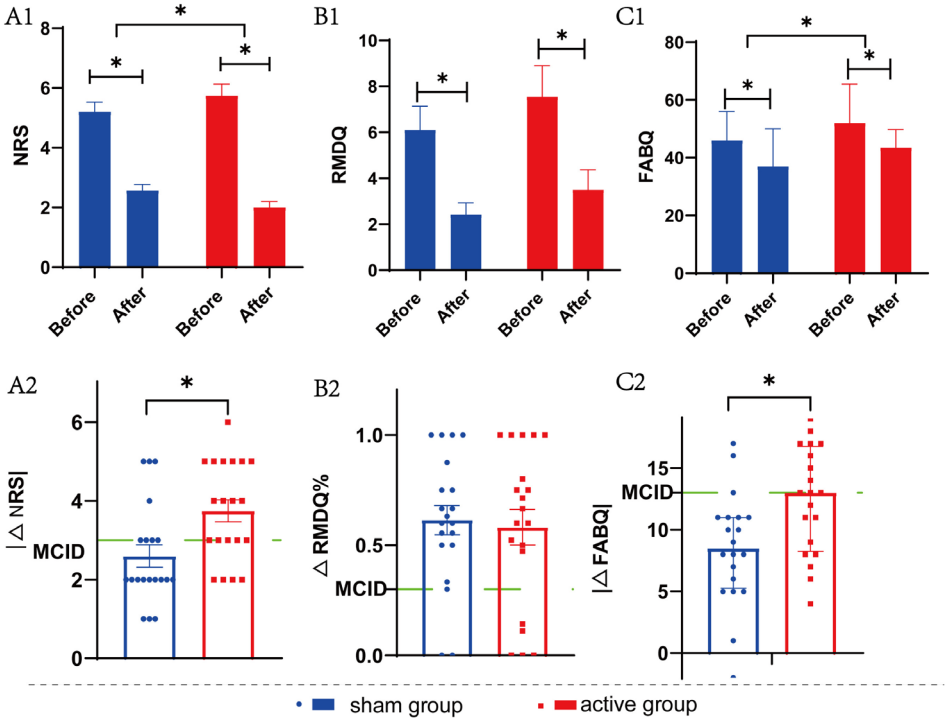

FIGURE 2 | Clinical scores before and after the intervention. NRS (A1), RMDQ (B1), and FABQ (C1) scores before and after the intervention. Changes in NRS (A2), RMDQ (B2), and FABQ (C2) scores after the intervention. The green dashed line shows the MCID for each scale. *$p < 0.05$. FABQ, Fear-Avoidance Beliefs Questionnaire; MCID, minimal clinically important difference; NRS, Numerical Rating Scale; RMDQ, Roland–Morris Disability Questionnaire.

The Mann–Whitney *U* test used to compare the differences in FABQ scores between the two groups revealed a significant difference between the groups ($Z = 2.55$, $p = 0.011$, and effect size of $r = 0.40$). The active group had a median score change of 13 (interquartile range: 8.25–16.75), whereas the sham group had a median score change of 8.5 (interquartile range: 5.25–11). The FABQ MCID was met by 11 out of 20 participants (55%) in the active group and 3 out of 20 participants (15%) in the sham group (Figure 2). The calculated NNT was 2.5, indicating that for every approximately three patients treated with the active intervention, one patient would achieve the FABQ MCID.

The ReHo values did not show a significant between-group difference before and after the intervention ($p > 0.05$). Neither the active nor sham groups showed statistically significant changes in ReHo values before and after the intervention ($p > 0.05$). The fALFF value was higher in the active group than in the sham group after the intervention ($t = -2.460$, $p = 0.023$), which was not observed before the intervention (Figure 3). However, neither the active nor sham groups showed statistically significant changes in fALFF values before and after the intervention ($p > 0.05$).

There was a significant increase in resting-state functional connectivity between the left DLPFC and the right cerebellum, left occipital gyrus, and right occipital gyrus within the global grey mask after intervention in the active group compared with the sham group (voxel-level, $p < 0.001$; cluster-level FWE, $p < 0.01$) (Table 3 and Figure 4).

3.4 | Correlation Between Clinical Scores and Brain Functional Connectivity

Spearman's correlation analysis showed significant negative correlations between NRS scores and resting-state functional connectivity between the left DLPFC and right cerebellum (rho = −0.55, $p = 0.008$); right occipital gyrus (rho = −0.439, $p = 0.041$); and left occipital gyrus (rho = −0.45, $p = 0.034$) (Figure 5). Spearman's analysis also showed a significant correlation between the changes in NRS and FABQ scores after the intervention (rho = 0.41, $p = 0.01$). However, there was no significant correlation between FABQ scores and brain functional connectivity ($p > 0.05$).

3.5 | Adverse Events

No serious adverse events were recorded during the study. One mild adverse event was reported in the experimental group in the form of a transient headache during the first intervention. This did not reoccur during subsequent treatments.

4 | Discussion

In this study, we investigated the efficacy and potential central mechanisms of a 4-week iTBS intervention in patients with CLBP. The results of the study showed that iTBS effectively alleviated pain-related clinical symptoms in patients with CLBP. The improvement in pain intensity was associated with increased functional connectivity between the DLPFC, cerebellum, and occipital gyrus. These novel findings suggest that iTBS may be a useful treatment for CLBP and indicate its potential underlying mechanism. We also found a significant correlation between changes in NRS and FABQ scores.

The finding that iTBS of the DLPFC in patients with CLBP alleviated pain and fear avoidance is consistent with the results of previous studies. Freigang et al. reported that 5 Hz rTMS applied to the DLPFC resulted in pain relief (Freigang et al. 2021). iTBS is an effective, non-invasive neuromodulation technique that has been shown to reduce the frequency of analgesic pump use after application to the DLPFC in patients with post-operative pain, suggesting potential analgesic effects (Cheng et al. 2023). A recent retrospective study found that iTBS of the DLPFC in patients with depression improved depressive symptoms and reduced pain scores (Kirupaharan et al. 2024), providing further evidence that iTBS of the DLPFC can alleviate pain.

Both groups in the present study demonstrated improvements in functional disability; however, there was no significant difference in the RMDQ scores between the active and sham iTBS groups. The RMDQ scores mainly reflect mobility and the ability to perform activities of daily living (Lin et al. 2011). A study conducted by Frizziero et al. (2021) demonstrated that CSE reduces functional disability in patients with CLBP. We speculate that the iTBS intervention primarily reduces pain intensity through modulation of pain-related brain networks, rather than

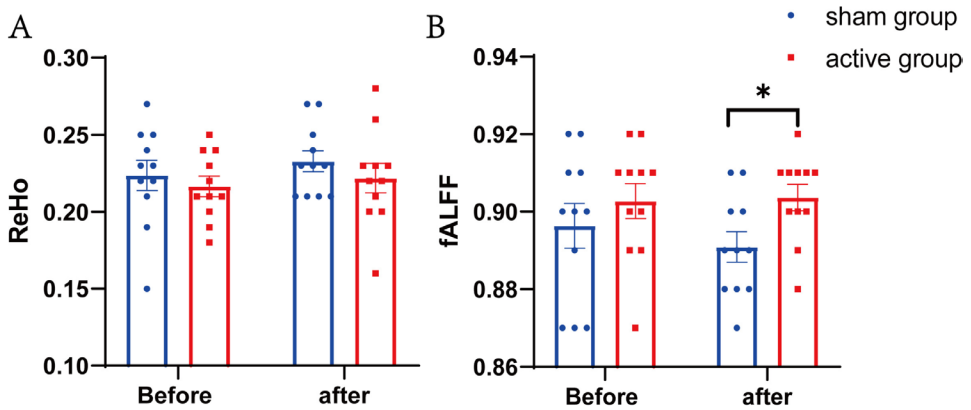

FIGURE 3 | (A) ReHo and (B) fALFF values of the left DLPFC before and after intervention. *$p < 0.05$. ReHo, regional homogeneity; fALFF, fractional amplitude of low-frequency fluctuations.

the ability to perform activities of daily living. Future studies are needed to compare the effects of iTBS and CSE on RMDQ scores.

TABLE 3 | Altered brain regions in seed-based resting-state functional connectivity after intervention.

Seed	Brain area	MNI coordinates			*T*	Cluster size (voxels)
		x	*y*	*Z*		
Active > sham						
L_DLPFC	Cerebelum_6_R	24	−33	−21	5.03	43
	Occipital_Mid_L	−51	−78	6	5.13	66
	Occipital_Mid_R	45	−69	15	6.2	47

Abbreviations: DLPFC, dorsolateral prefrontal cortex; L, left; Mid, middle; MNI, Montreal Neurologic Institute; R, right.

In the present study, the fMRI data indicated that iTBS of the DLPFC effectively activated the stimulation site by increasing the ALFF. These results are consistent with those of a previous study that showed increased activation in the left DLPFC following iTBS of this region (Chang et al. 2024). The DLPFC may affect pain by participating in multiple networks, such as controlling cognitive networks through modulation of the default mode network and extrinsic network switching, enhancing descending pain inhibitory pathway activation, or reducing the occurrence of negative emotions by regulating reward and fear circuits (Seminowicz and Moayedi 2017). The cerebellum, an important neural hub, receives efferents from the DLPFC engaged in cognitive control and pain modulation (Apkarian et al. 2004; Koechlin et al. 2003). In our study, the increased functional connectivity observed between the DLPFC and cerebellum was associated with reduced pain intensity, suggesting that the fronto-cerebellar circuit is involved in pain regulation. Our findings are supported by those of previous studies, which found that the fronto-cerebellar circuit serves as a key pathway for the non-motor functions of the

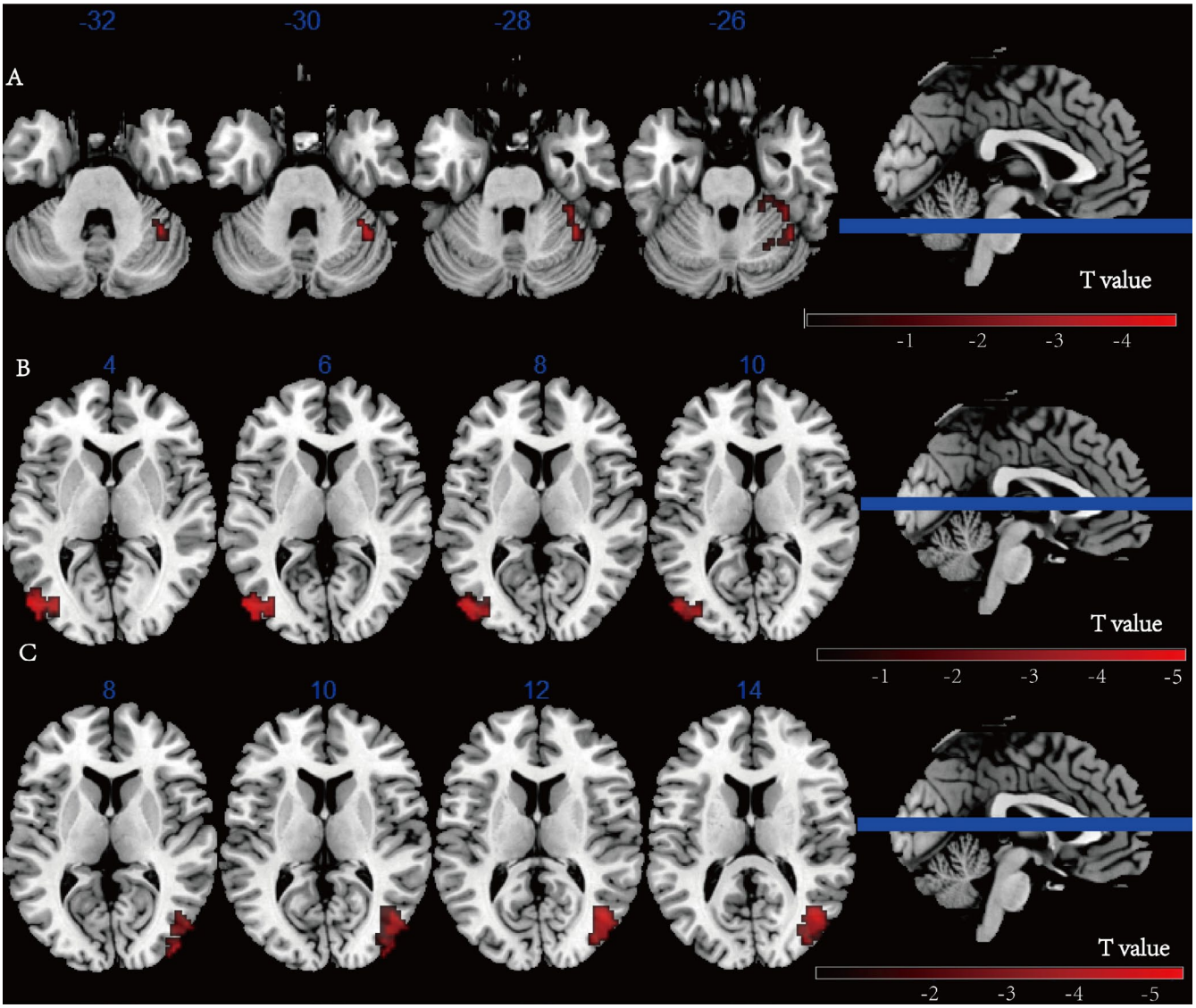

FIGURE 4 | Seed-based rs-FC changes between the left DLPFC and other brain regions after intervention. rs-FC between left DLPFC and right cerebellum (A), left DLPFC and left occipital gyrus (B), and left DLPFC and right occipital gyrus (C). DLPFC, dorsolateral prefrontal cortex; rs-FC, resting-state functional connectivity.

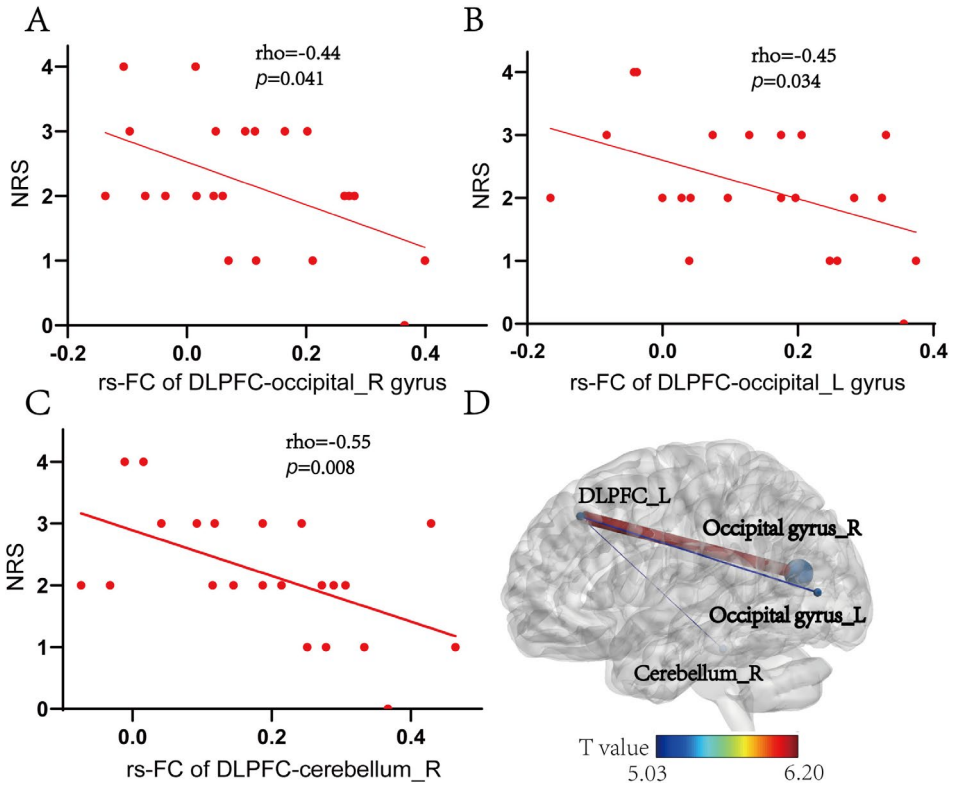

FIGURE 5 | Correlation between clinical scores and brain functional connectivity. Correlations between NRS scores and the rs-FC between the DLPFC and the right occipital gyrus (A), left occipital gyrus (B), and cerebellum (C). The rs-FC of the DLPFC with other brain regions increased significantly after intervention (D). DLPFC, dorsolateral prefrontal cortex; NRS, Numerical Rating Scale; rs-FC, resting-state functional connectivity.

cerebellum (Krienen and Buckner 2009). During pain processing, the cerebellum not only participates in sensory perception but is also involved in cognitive and emotional processes related to pain (Moulton et al. 2010). A previous study used fMRI to demonstrate extensively decreased functional connectivity among the anterior cingulate cortex, middle cingulate cortex, occipital gyrus, precentral gyrus, and cerebellum in patients with CLBP (Liu et al. 2018). A study conducted by Stacheneder et al. found that anodal transcranial direct current stimulation applied to the cerebellum could reduce pain perception and enhance the pain inhibition, possibly through the descending pain pathway (Stacheneder et al. 2023). In the present study, the 4-week iTBS intervention increased functional connectivity between the DLPFC and cerebellum, which may reduce pain perception and increase pain inhibition by the descending inhibitory pathway during pain processing.

In addition to the cerebellum, our study found that increased functional connectivity between the DLPFC and bilateral occipital gyri is associated with pain reduction. The activation of the occipital gyrus is significantly related to pain intensity (Kong et al. 2010), and in patients with CLBP, the activation of the occipital gyrus decreases as pain increases (Mayr et al. 2022). In postherpetic neuralgia, functional connectivity between the medial and lateral prefrontal cortices and the occipital cortex is related to pain scores, consistent with our previous findings (Li et al. 2018a). Interestingly, the occipital gyrus may be involved in the cognitive biases of patients with depression through its connections with the limbic and cortical regions (Zhang et al. 2022). Patients with mild cognitive impairment have been shown to exhibit decreased functional connectivity between the DLPFC and right occipital gyrus (Liang et al. 2011). However, the role of functional connectivity between the DLPFC and occipital gyrus in patients with CLBP remains unclear.

Evidence suggests that CSE can activate cortical or subcortical motor control networks (Kim et al. 2018). A separate study found that changes in activation within the frontal and occipital gyri are associated with cognitive tasks after exercise (Li et al. 2014), indicating an interaction between exercise and cognitive processes. In our study, combining iTBS with CSE increased functional connectivity between the DLPFC and the cerebellum, as well as between the DLPFC and the occipital lobe, compared with CSE and sham iTBS. We speculate that iTBS enhances the effects of CSE by increasing the functional connectivity between the DLPFC, occipital lobe, and cerebellum, thus enhancing cognitive networks in a compensatory manner. In future studies, a factorial design is required to verify this hypothesis.

Another study based on fMRI data reported that compared to healthy controls, patients with CLBP exhibited reduced grey matter volume in the right DLPFC, middle occipital gyrus, and cerebellum (Li et al. 2018b). The authors further discovered that, in patients with CLBP, certain areas of the right cerebellum (lobule VI) showed reduced functional connectivity with limbic regions, including the contralateral hippocampus and amygdala (Li et al. 2018b). A separate study found that patients with CLBP exhibited decreased functional connectivity between the DLPFC and the insula, which is associated with pain scores (Ceko et al. 2015), suggesting a role for the cerebellum in the emotional regulation of pain through a large-scale brain network.

Although our study identified between-group differences in the changes in FABQ scores after the intervention, we did not observe significant functional connectivity in the frontal-insular and cerebellum-limbic networks. This may be due to the small sample size decreasing the statistical power of the fMRI data.

Our study has certain limitations. First, due to the restrictions imposed during the COVID-19 pandemic, some participants were unable to undergo fMRI. The reduced sample size may have increased individual variability and decreased the statistical power. Future studies with larger sample sizes are required to confirm our findings. Second, the DLPFC has been reported to be involved in important cognitive and emotional processing (Seminowicz and Moayedi 2017). However, we did not find a significant correlation between FABQ scores and functional connectivity in the brain. This lack of a significant correlation may be due to the small sample size and the fact that the FABQ score was the only emotional outcome variable. Additionally, the improvement in NRS scores between the active and sham groups was marginally significant, which required further validation in a larger sample size in the future study. Third, considering the close relationship between anxiety and depression and the DLPFC, which may affect pain perception in individuals with CLBP, we excluded patients with anxiety and depression during the selection process (Du et al. 2018; White et al. 2023). This necessitates a more cautious interpretation of our study conclusions when applied to patients with CLBP accompanied by anxiety and depression. Future research should include such participants. Fourth, we did not assess the effectiveness of blinding in this experiment, which might increase the bias from subjective factors. In the future study, we should consider the blinding assessment. Finally, the participants in this study only had a very superficial pain description before and after the intervention. However, we did not collect the information, which involved the participants' current therapy, previous pain management approaches, or the impact of pain on quality of life, mood, sleep, and catastrophising, and so forth. The lack of these pain-related clinical outcomes may potentially affect the interpretation of our results. Future research should include more comprehensive pain assessments to show a better explanation of the effect of iTBS over DLPFC in CLBP patients.

In conclusion, the results of the present study showed that iTBS can alleviate pain in patients with CLBP by increasing functional connectivity between the DLPFC and the cerebellum and occipital gyrus.

Author Contributions

Jiajia Yang and Xiaoyu Gao: conceptualisation, methodology, formal analysis, writing – original draft. Xue Cheng: methodology, formal analysis, validation, investigation. Ruochen Fu: visualisation, validation. Hao Xie: data curation, formal analysis. Siyun Zhang: resources, software. Zhenwen Liang: software, original draft. Qiuhua Yu: funding acquisition, supervision, writing – review and editing. Xi Chen and Chuhuai Wang: funding acquisition, supervision.

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Disclosure

A statement about the originality of the work: This randomised controlled trial investigated the effects of intermittent theta burst stimulation (iTBS) of the dorsolateral prefrontal cortex (DLPFC), in combination with core stability exercise, on chronic low back pain.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Ambriz-Tututi, M., B. Alvarado-Reynoso, and R. Drucker-Colín. 2016. "Analgesic Effect of Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients With Chronic Low Back Pain." *Bioelectromagnetics* 37: 527–535. https://doi.org/10.1002/bem.22001.

Apkarian, A. V., Y. Sosa, S. Sonty, et al. 2004. "Chronic Back Pain Is Associated With Decreased Prefrontal and Thalamic Gray Matter Density." *Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 24: 10410–10415. https://doi.org/10.1523/jneurosci.2541-04.2004.

Ashburner, J. 2007. "A Fast Diffeomorphic Image Registration Algorithm." *NeuroImage* 38: 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Austin, P. C., I. R. White, D. S. Lee, and S. van Buuren. 2021. "Missing Data in Clinical Research: A Tutorial on Multiple Imputation." *Canadian Journal of Cardiology* 37: 1322–1331. https://doi.org/10.1016/j.cjca.2020.11.010.

Cardenas-Morales, L., D. A. Nowak, T. Kammer, R. C. Wolf, and C. Schonfeldt-Lecuona. 2010. "Mechanisms and Applications of Theta-Burst rTMS on the Human Motor Cortex." *Brain Topography* 22: 294–306. https://doi.org/10.1007/s10548-009-0084-7.

Ceko, M., Y. Shir, J. A. Ouellet, M. A. Ware, L. S. Stone, and D. A. Seminowicz. 2015. "Partial Recovery of Abnormal Insula and Dorsolateral Prefrontal Connectivity to Cognitive Networks in Chronic Low Back Pain After Treatment." *Human Brain Mapping* 36: 2075–2092. https://doi.org/10.1002/hbm.22757.

Chang, K. Y., M. Tik, Y. Mizutani-Tiebel, et al. 2024. "Dose-Dependent Target Engagement of a Clinical iTBS Protocol: An Interleaved TMS-fMRI Study in Healthy Subjects." *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, ahead of print, August 25. https://doi.org/10.1016/j.bpsc.2024.08.009.

Cheng, M., X. Che, Y. Ye, et al. 2023. "Analgesic Efficacy of Theta-Burst Stimulation for Postoperative Pain." *Clinical Neurophysiology* 149: 81–87. https://doi.org/10.1016/j.clinph.2023.02.174.

Chou, R., R. Deyo, J. Friedly, et al. 2017. "Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline." *Annals of Internal Medicine* 166: 493–505. https://doi.org/10.7326/m16-2459.

Dekker, J., M. de Boer, and R. Ostelo. 2024. "Minimal Important Change and Difference in Health Outcome: An Overview of Approaches, Concepts, and Methods." *Osteoarthritis and Cartilage* 32, no. 1: 8–17. https://doi.org/10.1016/j.joca.2023.09.002.

Du, L., H. Liu, W. Du, et al. 2018. "Stimulated Left DLPFC-Nucleus Accumbens Functional Connectivity Predicts the Anti-Depression and Anti-Anxiety Effects of rTMS for Depression." *Translational Psychiatry* 7: 3. https://doi.org/10.1038/s41398-017-0005-6.

Dworkin, R. H., D. C. Turk, K. W. Wyrwich, et al. 2008. "Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain

Clinical Trials: IMMPACT Recommendations." *Journal of Pain* 9: 105–121. https://doi.org/10.1016/j.jpain.2007.09.005.

Freigang, S., C. Lehner, S. M. Fresnoza, et al. 2021. "Comparing the Impact of Multi-Session Left Dorsolateral Prefrontal and Primary Motor Cortex Neuronavigated Repetitive Transcranial Magnetic Stimulation (nrTMS) on Chronic Pain Patients." *Brain Sciences* 11: 961. https://doi.org/10.3390/brainsci11080961.

Frizziero, A., G. Pellizzon, F. Vittadini, D. Bigliardi, and C. Costantino. 2021. "Efficacy of Core Stability in Non-Specific Chronic Low Back Pain." *Journal of Functional Morphology and Kinesiology* 6: 37. https://doi.org/10.3390/jfmk6020037.

George, S. Z., J. M. Fritz, and D. W. McNeil. 2006. "Fear-Avoidance Beliefs as Measured by the Fear-Avoidance Beliefs Questionnaire: Change in Fear-Avoidance Beliefs Questionnaire Is Predictive of Change in Self-Report of Disability and Pain Intensity for Patients With Acute Low Back Pain." *Clinical Journal of Pain* 22: 197–203. https://doi.org/10.1097/01.ajp.0000148627.92498.54.

Grossheinrich, N., A. Rau, O. Pogarell, et al. 2009. "Theta Burst Stimulation of the Prefrontal Cortex: Safety and Impact on Cognition, Mood, and Resting Electroencephalogram." *Biological Psychiatry* 65: 778–784. https://doi.org/10.1016/j.biopsych.2008.10.029.

Herwig, U., P. Satrapi, and C. Schonfeldt-Lecuona. 2003. "Using the International 10-20 EEG System for Positioning of Transcranial Magnetic Stimulation." *Brain Topography* 16: 95–99. https://doi.org/10.1023/b:brat.0000006333.93597.9d.

Huang, Y. Z., M. J. Edwards, E. Rounis, K. P. Bhatia, and J. C. Rothwell. 2005. "Theta Burst Stimulation of the Human Motor Cortex." *Neuron* 45: 201–206. https://doi.org/10.1016/j.neuron.2004.12.033.

Ihara, N., K. Wakaizumi, D. Nishimura, et al. 2019. "Aberrant Resting-State Functional Connectivity of the Dorsolateral Prefrontal Cortex to the Anterior Insula and Its Association With Fear Avoidance Belief in Chronic Neck Pain Patients." *PLoS One* 14: e0221023. https://doi.org/10.1371/journal.pone.0221023.

James, S. L., D. A. Abate, K. H. Abate, et al. 2018. "Global, Regional, and National Incidence, Prevalence, and Years Lived With Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017." *Lancet* 392: 1789–1858. https://doi.org/10.1016/s0140-6736(18)32279-7.

Jia, X. Z., J. Wang, H. Y. Sun, et al. 2019. "RESTplus: An Improved Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing." *Science Bulletin* 64: 953–954. https://doi.org/10.1016/j.scib.2019.05.008.

Jordan, K., K. M. Dunn, M. Lewis, and P. Croft. 2006. "A Minimal Clinically Important Difference Was Derived for the Roland-Morris Disability Questionnaire for Low Back Pain." *Journal of Clinical Epidemiology* 59: 45–52. https://doi.org/10.1016/j.jclinepi.2005.03.018.

Kim, D. H., J. J. Lee, and S. J. H. You. 2018. "Best Core Stabilization Exercise to Facilitate Subcortical Neuroplasticity: A Functional MRI Neuroimaging Study." *Technology and Health Care* 26: 401–407. https://doi.org/10.3233/THC-171051.

Kirupaharan, S., R. Milev, J. Bressee, et al. 2024. "Changes in Pain Following Bilateral Intermittent Theta-Burst, Transcranial Magnetic Stimulation for Depression: A Retrospective Chart Review." *Canadian Journal of Pain* 8: 2300026. https://doi.org/10.1080/24740527.2023.2300026.

Klomjai, W., R. Katz, and A. Lackmy-Vallée. 2015. "Basic Principles of Transcranial Magnetic Stimulation (TMS) and Repetitive TMS (rTMS)." *Annals of Physical and Rehabilitation Medicine* 58: 208–213. https://doi.org/10.1016/j.rehab.2015.05.005.

Koechlin, E., C. Ody, and F. Kouneiher. 2003. "The Architecture of Cognitive Control in the Human Prefrontal Cortex." *Science* 302: 1181–1185. https://doi.org/10.1126/science.1088545.

Kohútová, B., J. Fricová, M. Klírová, T. Novák, and R. Rokyta. 2017. "Theta Burst Stimulation in the Treatment of Chronic Orofacial Pain: A Randomized Controlled Trial." *Physiological Research* 66: 1041–1047. https://doi.org/10.33549/physiolres.933474.

Kong, J., M. L. Loggia, C. Zyloney, P. Tu, P. LaViolette, and R. L. Gollub. 2010. "Exploring the Brain in Pain: Activations, Deactivations and Their Relation." *Pain* 148: 257–267. https://doi.org/10.1016/j.pain.2009.11.008.

Kothari, S. F., J. U. Blicher, L. K. Dagsdottir, et al. 2022. "Facilitatory Effect of Intermittent Repetitive Transcranial Magnetic Stimulation on Perceptual Distortion of the Face." *Journal of Pain* 23: 1051–1059. https://doi.org/10.1016/j.jpain.2021.12.013.

Kregel, J., M. Meeus, A. Malfliet, et al. 2015. "Structural and Functional Brain Abnormalities in Chronic Low Back Pain: A Systematic Review." *Seminars in Arthritis and Rheumatism* 45: 229–237. https://doi.org/10.1016/j.semarthrit.2015.05.002.

Krienen, F. M., and R. L. Buckner. 2009. "Segregated Fronto-Cerebellar Circuits Revealed by Intrinsic Functional Connectivity." *Cerebral Cortex* 19: 2485–2497. https://doi.org/10.1093/cercor/bhp135.

Lancaster, J. L., D. Tordesillas-Gutiérrez, M. Martinez, et al. 2007. "Bias Between MNI and Talairach Coordinates Analyzed Using the ICBM-152 Brain Template." *Human Brain Mapping* 28: 1194–1205. https://doi.org/10.1002/hbm.20345.

Li, J., X. Huang, K. Sang, M. Bodner, K. Ma, and X. W. Dong. 2018a. "Modulation of Prefrontal Connectivity in Postherpetic Neuralgia Patients With Chronic Pain: A Resting-State Functional Magnetic Resonance-Imaging Study." *Journal of Pain Research* 11: 2131–2144. https://doi.org/10.2147/JPR.S166571.

Li, L., W. W. Men, Y. K. Chang, M. X. Fan, L. Ji, and G. X. Wei. 2014. "Acute Aerobic Exercise Increases Cortical Activity During Working Memory: A Functional MRI Study in Female College Students." *PLoS One* 9: e99222. https://doi.org/10.1371/journal.pone.0099222.

Li, T., S. Zhang, and J. Kurata. 2018b. "Suppressed Descending Pain Modulatory and Enhanced Sensorimotor Networks in Patients With Chronic Low Back Pain." *Journal of Anesthesia* 32: 831–843. https://doi.org/10.1007/s00540-018-2561-1.

Liang, P., Z. Wang, Y. Yang, X. Jia, and K. Li. 2011. "Functional Disconnection and Compensation in Mild Cognitive Impairment: Evidence From DLPFC Connectivity Using Resting-State fMRI." *PLoS One* 6: e22153. https://doi.org/10.1371/journal.pone.0022153.

Lin, C. C., J. H. McAuley, L. Macedo, D. C. Barnett, R. J. Smeets, and J. A. Verbunt. 2011. "Relationship Between Physical Activity and Disability in Low Back Pain: A Systematic Review and Meta-Analysis." *Pain* 152: 607–613. https://doi.org/10.1016/j.pain.2010.11.034.

Liu, J., F. Zhang, X. Liu, et al. 2018. "Altered Small-World, Functional Brain Networks in Patients With Lower Back Pain." *Science China. Life Sciences* 61: 1420–1424. https://doi.org/10.1007/s11427-017-9108-6.

Maher, C., M. Underwood, and R. Buchbinder. 2017. "Non-Specific Low Back Pain." *Lancet* 389: 736–747. https://doi.org/10.1016/s0140-6736(16)30970-9.

Mayr, A., P. Jahn, A. Stankewitz, et al. 2022. "Patients With Chronic Pain Exhibit Individually Unique Cortical Signatures of Pain Encoding." *Human Brain Mapping* 43: 1676–1693. https://doi.org/10.1002/hbm.25750.

Moulton, E. A., J. D. Schmahmann, L. Becerra, and D. Borsook. 2010. "The Cerebellum and Pain: Passive Integrator or Active Participator?" *Brain Research Reviews* 65: 14–27. https://doi.org/10.1016/j.brainresrev.2010.05.005.

Nugent, S. M., T. I. Lovejoy, S. Shull, S. K. Dobscha, and B. J. Morasco. 2021. "Associations of Pain Numeric Rating Scale Scores Collected During Usual Care With Research Administered Patient Reported Pain

Outcomes." *Pain Medicine* 22: 2235–2241. https://doi.org/10.1093/pm/pnab110.

Olechowski, C., M. Gener, R. Aiyer, and N. Mischel. 2023. "Transcranial Magnetic Stimulation for the Treatment of Chronic Low Back Pain: A Narrative Review." *Frontiers in Pain Research* 4: 1092158. https://doi.org/10.3389/fpain.2023.1092158.

Ong, W. Y., C. S. Stohler, and D. R. Herr. 2019. "Role of the Prefrontal Cortex in Pain Processing." *Molecular Neurobiology* 56: 1137–1166. https://doi.org/10.1007/s12035-018-1130-9.

Ostelo, R. W., R. A. Deyo, P. Stratford, et al. 2008. "Interpreting Change Scores for Pain and Functional Status in Low Back Pain: Towards International Consensus Regarding Minimal Important Change." *Spine* 33: 90–94. https://doi.org/10.1097/BRS.0b013e31815e3a10.

Sahu, A. K., V. K. Sinha, and N. Goyal. 2019. "Effect of Adjunctive Intermittent Theta-Burst Repetitive Transcranial Magnetic Stimulation as a Prophylactic Treatment in Migraine Patients: A Double-Blind Sham-Controlled Study." *Indian Journal of Psychiatry* 61: 139–145. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_472_18.

Seminowicz, D. A., and M. Moayedi. 2017. "The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain." *Journal of Pain* 18: 1027–1035. https://doi.org/10.1016/j.jpain.2017.03.008.

Stacheneder, R., L. Alt, A. Straube, and R. Ruscheweyh. 2023. "Effects of Transcranial Direct Current Stimulation (t-DCS) of the Cerebellum on Pain Perception and Endogenous Pain Modulation: A Randomized, Monocentric, Double-Blind, Sham-Controlled Crossover Study." *Cerebellum* 22: 1234–1242. https://doi.org/10.1007/s12311-022-01498-x.

Takano, M., J. Havlicek, D. Phillips, S. Nakajima, M. Mimura, and Y. Noda. 2021. "Development of an Advanced Sham Coil for Transcranial Magnetic Stimulation and Examination of Its Specifications." *Journal of Personalized Medicine* 11: 1058. https://doi.org/10.3390/jpm11111058.

Tzourio-Mazoyer, N., B. Landeau, D. Papathanassiou, et al. 2002. "Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain." *NeuroImage* 15: 273–289. https://doi.org/10.1006/nimg.2001.0978.

Urits, I., A. Burshtein, M. Sharma, et al. 2019. "Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment." *Current Pain and Headache Reports* 23: 23. https://doi.org/10.1007/s11916-019-0757-1.

van der Roer, N., R. W. Ostelo, G. E. Bekkering, M. W. van Tulder, and H. C. de Vet. 2006. "Minimal Clinically Important Change for Pain Intensity, Functional Status, and General Health Status in Patients With Nonspecific Low Back Pain." *Spine (Phila Pa 1976)* 31: 578–582. https://doi.org/10.1097/01.brs.0000201293.57439.47.

Wang, H., Z. Fan, X. Liu, et al. 2023. "Effect of Progressive Postural Control Exercise Versus Core Stability Exercise in Young Adults With Chronic Low Back Pain: A Randomized Controlled Trial." *Pain and Therapy* 12: 293–308. https://doi.org/10.1007/s40122-022-00458-x.

White, L. K., W. Makhoul, M. Teferi, Y. I. Sheline, and N. L. Balderston. 2023. "The Role of dlPFC Laterality in the Expression and Regulation of Anxiety." *Neuropharmacology* 224: 109355. https://doi.org/10.1016/j.neuropharm.2022.109355.

Yang, C., Y. Bi, L. Hu, et al. 2023. "Effects of Different Transcranial Magnetic Stimulations on Neuropathic Pain After Spinal Cord Injury." *Frontiers in Neurology* 14: 1141973. https://doi.org/10.3389/fneur.2023.1141973.

Yu, Q., F. Herold, B. Becker, et al. 2021. "Cognitive Benefits of Exercise Interventions: An fMRI Activation Likelihood Estimation Meta-Analysis." *Brain Structure & Function* 226: 601–619. https://doi.org/10.1007/s00429-021-02247-2.

Yuan, C., H. Shi, P. Pan, et al. 2017. "Gray Matter Abnormalities Associated With Chronic Back Pain: A Meta-Analysis of Voxel-Based Morphometric Studies." *Clinical Journal of Pain* 33: 983–990. https://doi.org/10.1097/ajp.0000000000000489.

Zeng, X., W. Tang, J. Yang, et al. 2023. "Diagnosis of Chronic Musculoskeletal Pain by Using Functional Near-Infrared Spectroscopy and Machine Learning." *Bioengineering* 10: 669. https://doi.org/10.3390/bioengineering10060669.

Zhang, X., R. Zhang, L. Lv, X. Qi, J. Shi, and S. Xie. 2022. "Correlation Between Cognitive Deficits and Dorsolateral Prefrontal Cortex Functional Connectivity in First-Episode Depression." *Journal of Affective Disorders* 312: 152–158. https://doi.org/10.1016/j.jad.2022.06.024.

Zhou, J., Y. Wang, X. Luo, et al. 2024. "Revisiting the Effects of rTMS Over the Dorsolateral Prefrontal Cortex on Pain: An Updated Systematic Review and Meta-Analysis." *Brain Stimulation* 17: 928–937. https://doi.org/10.1016/j.brs.2024.07.011.