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Feasibility, Safety, and Preliminary Efficacy of Intermittent Theta Burst Stimulation Targeting the Left Dorsolateral Prefrontal Cortex in Older Adults with Chronic Low Back Pain with or without Comorbid Chronic Knee Pain: A Pilot Randomized Sham- Controlled Trial

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Abstract

Background

Chronic back and knee pain are associated with executive dysfunction in older adults. Intermittent theta burst stimulation (iTBS) over the left dorsolateral prefrontal cortex (L-DLPFC) may modulate pain and cognitive networks, but its application in this population is underexplored.

Methods

This pilot randomized, double-blind, sham-controlled trial evaluated the feasibility, safety, and preliminary clinical/neural effects of repeated L-DLPFC iTBS in older adults with chronic pain. Thirty participants (aged 60–85 years) were randomized to receive 12 sessions of active or sham iTBS over two weeks. Primary outcomes were feasibility and acceptability. Trial progression viability was evaluated using traffic light system. Secondary outcomes included patient-reported pain intensity, disability, and negative thoughts, alongside executive function performance and task-based functional magnetic resonance imaging.

Results

The protocol met “Green (Go)” criteria, demonstrating high feasibility and acceptability: the trial achieved an 8.1% recruitment rate, a 93.3% completion rate (6.7% attrition rate), an overall acceptability score (33.1 ± 3.7) significantly above the scale midpoint, and no serious adverse events. Both groups reported reduced chronic low back pain intensity across follow-ups ($P_{FDR-corrected} < 0.001$), while knee pain intensity remained unchanged. Unexpectedly, fewer response inhibition errors in executive function were observed primarily in the sham group ($P_{FDR-corrected} = 0.01$). Neuroimaging results showed that the active group modulated frontoparietal activity during cognitive switching task. Qualitative interviews identified perceived cognitive/pain benefits, barriers, and optimization suggestions.

Conclusions

Meeting all pre-specified “Green (Go)” progression criteria confirms that iTBS over the left DLPFC is feasible and well-tolerated for older adults with chronic pain and executive dysfunction. Active stimulation uniquely modulated frontoparietal activity during cognitive switching. Further large-scale RCTs with neuroimaging are warranted to elucidate the neurophysiological basis of treatment efficacy.

Trial registration:

ClinicalTrials.gov (NCT06709963).

1. Introduction

Chronic musculoskeletal pain (CMP), predominantly chronic low back pain (CLBP) and chronic knee pain (CKP), represents a heavy global health crisis among older adults, contributing significantly to morbidity, mortality, and escalating healthcare costs.[1] Emerging evidence indicates that CLBP and CKP are not only peripheral conditions but are intrinsically linked to accelerated cognitive decline, especially in the domains of memory and executive function.[2, 3] This intersection of chronic pain and cognitive impairment creates a “double burden” for older adults, necessitating therapeutic strategies that transcend traditional analgesia to address the shared neural substrates of pain and cognition.

The management of comorbid CLBP/CKP and executive dysfunction presents a significant clinical challenge. While lifestyle modifications (e.g., smoking cessation, physical activity, sleep hygiene) are beneficial in mitigating cognitive decline in older adults with chronic pain,[4, 5] the optimal management strategies for this population remain elusive. Current neurobiological models suggest that chronic pain-related cognitive impairment is attributed to the "distraction effects" of persistent nociceptive input and aberrant functional connectivity within the brain, often associated with central sensitization.[6, 7] Given the heightened risk of polypharmacy and adverse drug reactions in older adults, non-pharmacological interventions are increasingly prioritized.[8] Consequently, there is an urgent need for interventions capable of directly modulating the maladaptive neuroplasticity underlying both CMP and cognitive decline.

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a potent non-invasive neuromodulation technique for modulating cortical excitability and improving both pain and cognitive symptoms.[9–11] Intermittent theta burst stimulation (iTBS) represents a significant advancement in this field by mimicking endogenous theta rhythms. iTBS delivers 600 pulses in just 3 minutes to generate neuromodulating effects comparable to conventional rTMS in a fraction of the time,[12, 13] thereby enhancing its clinical utility for older adults. The left dorsolateral prefrontal cortex (L-DLPFC) is a critical neuroanatomical target, as it serves as a key regulator for both top-down inhibitory pain pathways and executive control networks.[14] Preliminary research suggests that iTBS targeting L-DLPFC (L-DLPFC-iTBS) can improve pain and balance in individuals with CLBP, potentially by enhancing functional connectivity between the L-DLPFC, cerebellum, and occipital gyrus.[15, 16] Additionally, L-DLPFC-iTBS has shown promise in enhancing memory in early-stage Alzheimer's disease by increasing cortical excitability and beta oscillatory activity.[17] However, it remains uncertain whether L-DLPFC-iTBS can concurrently alleviate pain and improve executive function in older adults presenting with complex CMP profiles.

Despite the therapeutic promise, the feasibility, safety, and mechanistically driven effects of L-DLPFC-iTBS have not been rigorously evaluated in older adults with varying CMP distributions. This double-blind, sham-controlled pilot randomized controlled trial (RCT) aimed to assess the feasibility, acceptability, and preliminary effects of a 12-session L-DLPFC-iTBS protocol on clinical outcomes and neural signatures in older adults with CLBP, including those with comorbid CKP.

2. Methods

2.1. Study design

This two-arm, double-blind, sham-controlled pilot RCT followed the CONSORT 2010 statement: extension to randomized pilot and feasibility trials.[18] This study was approved by the Institutional Review Board (HSEARS20240411013), registered at *ClinicalTrials.gov* (NCT06709963), and conducted at The Hong Kong Polytechnic University (PolyU) (between September 2024 and June 2025) in accordance with the Declaration of Helsinki.[19]

2.2. Participants

Community-dwelling older adults (aged 60–85 years) were recruited via community centers. Inclusion criteria were: (1) chronic nonspecific low back pain, with or without CKP, for ≥ 3 months;[20] (2) mean pain intensity of ≥ 4/10 on an 11-point numerical pain rating scale (NPRS) over the last 7 days (0 means "no pain" and 10 means "worst pain imaginable");[21] (3) pain on ≥ 50% of days in the past 4 weeks;[22] (4) normal cognitive function (Hong Kong Montreal Cognitive Assessment or its alternate versions) ≥ 26) (avoiding the practice effect);[23, 24] (5) right-handedness;[25] (6) fluency in Cantonese; (7) ≥ 6 years of formal education with Chinese literacy; (8) capacity to provide written informed consent, complete experimental testing, and communicate via email or text message for electronic data collection; and (9) no prior history of iTBS treatment.

Exclusion criteria were contraindications for magnetic resonance imaging (MRI) or rTMS (e.g., seizures, claustrophobia, or cochlear implants that are close to the TMS coil),[26] inability to ambulate independently (canes or walkers were

allowed), specific spinal pathology (e.g., spinal stenosis, spondylolisthesis), other concurrent musculoskeletal pain with an average pain intensity ≥ 4/10 (e.g., fibromyalgia, neck pain), severe neurological or psychiatric disorders, cognition-affecting medications or addiction (e.g., benzodiazepines, anticonvulsants, drug or alcohol addiction), or specific inflammatory disorders (e.g., rheumatoid arthritis, rheumatica).

2.3. Sample size calculation

Sample size was determined according to pilot RCT guidelines,[27] which recommend 10–15 participants per arm. Accordingly, 30 participants (about 15 per group) were enrolled.

2.4. Procedure

Before enrollment, all potential participants were screened for contraindications and risks of adverse events using a standardized rTMS screening questionnaire.[28] Eligible participants provided informed consent and were randomly assigned to receive 12 sessions of active or sham iTBS over two weeks. Assessments occurred at baseline, immediately post-treatment, and at one- and three-month follow-ups. To maximize retention, the self-reported outcome assessment at three-month follow-up was conducted either online or face-to-face based on participant preference (Fig. 1).

2.5. Randomization and blinding

Participants were randomized (1:1) to active or sham iTBS using block randomization (block sizes of four and six). Allocation was managed by an independent researcher who generated a random allocation sequence using Microsoft Excel, and then concealed it using sequentially numbered, opaque, sealed envelopes.[29] Participants and two outcome assessors were blinded to group assignment.

2.6. Interventions

Both active and sham interventions were administered using a MagPro X100 magnetic stimulator (Tonica Electronic, Farum, Denmark) with a figure-of-eight active/placebo coil (Cool-B65 A/P). Participants seated comfortably in a semi-reclined position and instructed to relax throughout the procedure. Participants received two sessions per day (15-minute interval), three days per week, for two weeks (total 12 sessions; 1,200 pulses/day) according to the recommended rTMS protocol for analgesia.[30] The interventions were delivered by experienced professionals who completed standardized rTMS training to ensure protocol fidelity. Participants were instructed not to initiate any new pain or rehabilitation interventions during the study period until the completion of three-month follow-up.

2.6.1. Active iTBS targeting L-DLPFC group

Each session comprised 30 pulses per 2-second train (ten 50 Hz triplets at 5 Hz), with trains delivered every 10 seconds (2 seconds on, 8 seconds off), totaling 600 pulses per session. day.[15] Each treatment session lasted approximately 21 minutes. Stimulation intensity was set at 70% of each participant's resting motor threshold, determined over the primary motor cortex using standard procedures.[31] The motor threshold was defined as the minimum intensity required to elicit motor evoked potentials of at least 50 uV in the right first dorsal interosseous muscle in at least 5 out of 10 consecutive trials.[32]

Each participant was given iTBS over the L-DLPFC.[15] The L-DLPFC was located in the middle frontal gyrus and corresponds to the lateral part of Brodmann Areas 9 and 46.[33] The target location was determined using the neuronavigational system (LOCALITE R © TMS Navigator Germany) based on participants' T1-weighted anatomical MRI brain scan [Montreal Neurological Institute coordinates (x, y, z = -38, 44, 26)].

2.6.2. Sham iTBS group

Participants received sham iTBS over the L-DLPFC. The sham stimulation was delivered using a placebo coil system, which produces similar auditory and somatosensory sensations as the active coil without inducing a significant electric field in the cortex.[34] The stimulation parameters for the sham condition were identical to the intervention group.

2.7. Primary outcomes

Feasibility was assessed by recruitment, completion, and attrition rates,[35] as well as blinding effectiveness. Non-completion reasons were also documented. The post-treatment blinding effectiveness was assessed by asking participants to guess their group allocation (active iTBS, sham, or unsure). Those who guessed active or sham stimulation were asked to provide reasons for their conjecture.

Acceptability was evaluated by a 15-item acceptability questionnaire and adverse events. Each item in the acceptability questionnaire was rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). It includes a positive subscale (10 items) and a negative subscale (5 items), yielding a total score ranging from 15 to 75, with positive and negative subscale scores ranging from 10–50 and 5–25, respectively.[36] An overall acceptability score was then computed as the average of the positive and reverse-scored negative subscale totals (i.e., [positive + reverse-scored negative]/2). The composite scores range from 7.5 to 37.5, with higher values indicating greater treatment acceptability. Adverse events (e.g., pain at the stimulation site, post-treatment headaches, neck pain, seizure, muscle twitching, or toothache) were documented.[37]

To determine the feasibility of a future full-scale RCT, a Red-Amber-Green traffic light system was applied to the prespecified progression criteria.[18] Based on prior brain stimulation pilot study and the MRI scanning slot availability at PolyU,[38] the pre-established thresholds were defined as follows: (1) Green (Go): Fully feasible without modifications. This required achieving a recruitment rate of ≥ 8%, a completion rate of ≥ 80%, and an attrition rate of ≤ 20%. Meeting all three criteria supports proceeding to the definitive RCT; (2) Amber (Amend): Feasible but requires protocol modifications. This status is triggered if any metric falls slightly below the green thresholds (e.g., completion rate 70%-79%, or attrition rate 21%-29%), or if significant operational bottlenecks in MRI scheduling occur; (3) Red (Stop): Not feasible in its current form. This is triggered by unacceptable operational metrics (e.g., completion rate < 70% or attrition rate > 30%), requiring a substantial redesign of the study.

2.8. Secondary outcomes

2.8.1. Patient-reported clinical outcomes

A 11-point NPRS was used to assess the current pain intensity and the average pain intensity of CLBP and CKP over the past seven days.[39] Pittsburgh Sleep Quality Index (PSQI),[40] Hong Kong Chinese Version of the Roland-Morris Disability Questionnaire (RMDQ-HK),[41] Chinese version of Pain Catastrophizing Score,[42] and Western Ontario and McMaster Universities Osteoarthritis Index[43] were used to assess sleep quality, CLBP-related disability, chronic pain-related negative thoughts, and CKP-related disability, respectively, from baseline to follow-ups. Chinese version of the short Depression Anxiety Stress Scales,[44] Fatigue, Resistance, Ambulation, Illness, and Loss (FRAIL),[45] and Physical Activity Scale for the Elderly[46] were used to assess negative emotional states, frailty status, and physical activity levels at baseline. These questionnaires have been cross-culturally adapted into a traditional Chinese version with acceptable reliability and validity.[39–46]

2.8.2. Executive function performances

To evaluate executive function, a 30-minute neuropsychological battery was administered during functional MRI (fMRI) scanning using E-Prime 3.0 (Psychology Software Tools, Inc).[47] The battery comprised a Color-Word Matching Stroop Task (event-related design),[48, 49] a More-Odd-Shifting Task (event-related design),[48, 50] and a Digit 2-Back Task (block design) (Fig. 1).[51, 52] Details are summarized in Supplementary Methods 1.

2.9. Exploration of fMRI outcomes

Task-based fMRI data were acquired both before and after the intervention. All structural and functional MRI data were acquired on a 3.0T magnetic resonance scanner (MAGNETOM, Prisma, Siemens, Erlangen, Germany) at the University Research Facility in Behavioral and Systems Neuroscience of PolyU with a standard 32-channel head coil. Details are summarized in Supplementary Methods 2, Tables S1-S3 and Figures S1-S3.

2.10. Qualitative interviews

At the 3-month follow-up post-intervention, participants in the active group (n = 14) were invited to participate in individual semi-structured Zoom interviews (approximately 25 minutes each). Ten participated in the interviews, while four (28.6%) declined: reasons included time conflicts (n = 2); unwillingness to be interviewed (n = 1); and non-responsiveness to follow-up messages (n = 1). All participants provided informed consent. Interviews were audio-recorded and conducted between May and June 2025. A semi-structured interview guide was used to systematically collect data regarding participants' perceived changes, feedback on experimental procedures, and suggestions for future studies (Supplementary Methods 3).

2.11. Statistical analyses

A blinded researcher (FH) conducted the data analyses. Analyses followed an intention-to-treat analysis principle using R (version 4.4.2) and SPM12.[53, 54] Normality of continuous variables was assessed using the Shapiro-Wilks test; non-normally distributed variables were log-transformed or reported as medians with interquartile ranges. A two-sided *P* value < 0.05 was considered statistically significant. There were no missing data for the primary and secondary outcomes in this trial.

2.11.1. Primary outcomes

A one-sample t-test was performed on the overall acceptability scores (range 7.5–37.5) to test whether the mean exceeded the midpoint of 22.5. Higher scores reflect greater treatment acceptability.

2.11.2. Secondary outcomes

Baseline characteristics were compared between groups using Fisher's exact test for categorical variables. For continuous variables, independent t-tests were used for parametric variables, while Mann-Whitney U-tests were used for non-parametric variables. for. Blinding effectiveness was analyzed using Fisher's exact test.

To explore intervention effects on secondary outcomes (pain intensity, disability, negative thoughts, psychological status, frailty, physical activity, and sleep quality), we fitted linear mixed-effects models for each outcome. Models included group (active vs sham), time (pre-treatment, post-treatment, follow-ups), and their interaction as fixed effects. Where applicable, we adjusted for baseline characteristics showing significant between-group differences. Model selection was based on the lowest Akaike information criterion.[55] Executive function was analyzed via analysis of covariance, similarly adjusting for baseline imbalances.[56] Treatment effect sizes were estimated using Hedges' *g* with 95% confidence intervals for pairwise comparisons of temporal changes.[57] The Benjamini-Hochberg procedure was applied to control for the false positive rate (FDR) across multiple comparisons.[58] Effect sizes were interpreted as small (d > 0.2), medium (d > 0.5), or large (d > 0.8).[57]

2.11.3. Imaging data analysis

General linear models were constructed for each cognitive task.[59] At the first level, a single contrast image was generated per participant. Second-level analyses were performed to evaluate intervention effects (Supplementary Methods 2). A two-way mixed-design analysis of covariance was conducted with group as the between-subject factor and time as the within-subject factor, adjusting for baseline imbalances in relevant covariates.[56] The primary analytical

step was to test the group-by-time interaction. When the interaction was significant ($P < 0.05$), simple effects were systematically examined: (a) within-group neural activity changes over time were assessed separately for each group using paired-samples t-tests; and (b) between-group neural activity differences at each time point (pre-treatment and post-treatment) were evaluated using independent-samples t-tests. When the interaction was non-significant ($P \geq 0.05$), the analysis proceeded to interpret the main effects. Specifically, the main effect of time was examined to determine whether the neural activity changed significantly over time across both groups combined, and the group main effect was examined to determine whether neural activity differed between the two groups when averaged across the two time points.

2.11.4. Correlations of changes in neural activity and clinical outcomes

To explore associations between changes in neural activity and corresponding clinical outcome changes (NPRS, RMDQ-HK, FRAIL, and PSQI scores), partial correlation analyses were conducted for each group.[60]

2.11.5. Sensitivity analysis

We performed a sensitivity analysis on patient-reported outcomes (i.e., NPRS, RMDQ-HK, PSQI) using a per-protocol approach, including participants who fully adhered to the intervention without major deviations.[61]

2.11.6. Qualitative data analysis

Audio records of interviews were transcribed verbatim in Chinese. We employed an inductive thematic analysis approach.[62] Two researchers (FH and TC) engaged in a line-by-line coding of the transcripts using NVivo Version 12 software.[63] Discrepancy in coding was resolved through discussion. The inter-rater reliability was 89.8% between the two researchers. The final codebook was developed as a comprehensive summary of the identified themes and subtheme. [64]

3. Results

3.1. Feasibility and acceptability

During the 9-month recruitment period, 370 candidates were screened via the telephone (approximately 10.2 per week) yielding 125 (33.8%) individuals for further in-person screening. Of them, 95 were excluded due to psychiatric or neurological comorbidities (n = 25), MRI or iTBS contraindications (n = 20), fear of stimulation (n = 12), claustrophobia (n = 10), history of cancer (n = 5), and non-responsiveness (n = 23).Thirty eligible participants [CLBP (n = 17), comorbid CLBP and CKP (n = 13)] were randomized to active L-DLPFC-iTBS (n = 14) or sham-iTBS (n = 16) (Fig. 2). The pilot trial achieved a recruitment rate of 8.1%, a completion rate of 93.3%, and an attrition rate of 6.7%; since all three metrics successfully met the pre-specified “Green (Go)” thresholds, the feasibility of the protocol is fully demonstrated, supporting progression to the definitive full-scale RCT. Two withdrawals occurred: one loss-to-follow-up (active) and one due to fear of stimulation (sham). Treatment acceptability was high (mean = 33.1, standard deviation = 3.7), significantly exceeding the scale midpoint. Baseline characteristics were balanced between groups (Table 1).

Table 1
Demographic and clinical characteristics.

Gender (Female/Male)	**Active group (n = 14)**	**Sham group (n = 16)**	**FET / t/ M-WU**	***P***
	11/3	**14/2**	**2.273**	**0.654**
Age, median (IQR)	67.00 (64.00–70.00)	69.00 (66.90–71.10)	0.701	0.490
Height, median (IQR)	158.00 (153.10-162.90)	154.50 (150.10-158.90)	225.0[a]	0.755
Weight, median (IQR)	48.20 (35.20–61.30)	57.20 (51.10–63.30)	193.5[a]	0.339
Body Mass Index, median (IQR)	21.50 (17.60–25.40)	23.50 (22.00–25.00)	188.0[a]	0.750
Years of education, median (IQR)	11.00 (8.40–13.60)	13.50 (10.80–16.20)	2.242	**0.033***
Educational level [b], %	71.40	43.80	1.250	0.376
Primary educational level	14.30	31.20		
Secondary educational level	14.30	25.00		
Tertiary educational level				
Working status, %	0.00	12.50	0.000	0.639
Employed	85.70	81.50		
Retired	14.30	6.20		
Unemployed				
Marriage status, %	7.10	6.20	0.000	0.187
Divorced	57.10	75.00		
Married	28.60	0.00		
Single	7.10	18.80		
Widowed				
With high cholesterol, %	21.40	31.20	0.675	0.715
With hypertension, %	14.30	18.80	0.593	0.672
With endocrine disorders, %	14.30	12.50	1.161	1.000
With other diseases, %	14.30	18.80	0.593	0.672
Use of cardiovascular medications, %	14.30	12.50	1.161	1.000
Use of pain medications, %	0.000	18.80	0.000	0.113
Use of thyroid and gastrointestinal medications, %	14.30	12.50	1.161	1.000
Smoking frequency, %	92.90	93.80	1.138	1.000
Never	7.10	6.20		

Gender (Female/Male)	**Active group (n = 14)**	**Sham group (n = 16)**	**FET / t/ M-WU**	***P***
	11/3	**14/2**	**2.273**	**0.654**
Quitted	0.00	0.00		
Currently smoking				
Drinking frequency, %	85.70	87.50	0.000	1.000
Never	7.10	6.20		
Quitted	7.10	6.20		
Currently drinking				
Vision, %	7.10	25.00	2.273	0.654
Normal	92.90	75.00		
Normal after correction				
DASS-21, median (IQR)	6.50 (-2.40-15.40)	6.50 (1.50–11.50)	221.5[a]	0.868
Total score	3.00 (0.10–5.90)	3.00 (0.20–5.80)	226.5[a]	0.706
Depression sub-score	2.50 (-0.40-5.40)	3.00 (1.50–4.50)	218.5[a]	0.967
Anxiety sub-score	2.00 (-0.80-4.80)	1.50 (-0.90-3.90)	219.0[a]	0.949
Stress sub-score				
FRAIL Scale, median (IQR)	1.00 (-0.50-2.50)	1.00 (0.00–2.00)	227.0[a]	0.683
PASE, median (IQR)	103.70 (59.00-148.50)	114.70 (74.00-155.30)	-0.359	0.723
PSQI, median (IQR)	7.50 (5.40–9.60)	10.50 (7.10–13.90)	1.606	0.120
Duration of back pain (years), median (IQR)	5.00 (1.80–8.20)	6.50 (1.10–11.90)	123.00[a]	0.660
NPRS,	5.00 (4.00–6.00)	6.00 (5.20–6.80)	0.964	0.344
Average pain intensity of chronic back pain, One-week average, median (IQR)	5.00 (4.10–5.90)	6.00 (5.20–6.80)	146.50[a]	0.147
Currently, median (IQR)				
RMDQ, median (IQR)	8.00 (3.80–12.20)	8.50 (4.40–12.60)	-0.226	0.823
PCS, median (IQR)	19.00 (8.20–29.80)	21.50 (11.90–31.10)	0.988	0.332
		Without chronic knee pain (n = 15)	Chronic knee pain (n = 15)	

Gender (Female/Male)	Active group (n = 14)	Sham group (n = 16)		FET / t/ M-WU	*P*
	11/3	**14/2**		**2.273**	**0.654**
Duration of knee pain (years), median (IQR)	/	/	5.00 (2.00–8.00)	/	/
NPRS, Average pain intensity of chronic knee pain, median (IQR) One-week average, median (IQR) Currently	/	/	5.00 (4.20–5.80) 5.00 (4.20–5.80)	/	/
WOMAC, median (IQR) WOMAC total score WOMAC pain subscore WOMAC stiffness subscore WOMAC physical function subscore	/	/	34.00 (20.80–47.20) 9.00 (6.50–11.50) 3.00 (1.20–4.80) 22.00 (12.00–32.00)	/	/

Adverse events were mild and transient, including headaches (active n = 1, sham n = 2; NPRS scores ranging from 3 to 5), tinnitus (active n = 1), periocular pain (active n = 1; NPRS = 3), and dental root pain (sham n = 1; NPRS = 3). Regarding blinding, 62.1% (18/29) of participants who completed the study were unsure of their allocation. Eleven participants made definitive guesses and gave reasons due to: perceived head stimulation (36.36%), changes in CLBP intensity (45.45%), or belief that the protocol constituted active treatment (18.18%). Fisher's Exact Test yielded no significant between-group difference in guess distribution (Table S4).

3.2. Patient-reported outcome measures

No significant group-by-time interactions were observed for any patient-reported outcome measures ($P > 0.05$). Both groups showed no significant between-group differences in the patient-reported outcome measures at the baseline level (all $P > 0.05$). Only CLBP intensity and PSQI showed significant temporal changes (Time $P < 0.05$). Main effects of time were observed for CLBP intensity: both groups exhibited significant reductions in average one-week and current pain immediately post-treatment and at follow-ups ($P_{FDR-corrected} < 0.001$), although these changes did not reach the minimal clinically important difference (MCID). Notably, sleep quality (PSQI) deteriorated significantly in the active group ($P_{FDR-corrected} = 0.02$), but this change was not clinically significant. No other significant within- or between-group differences were found (Table 2, Fig. 3).

Table 2
Medians, interquartile range, and effect sizes for patient-reported outcome measures.

Outcome measures	Active group (n = 14)	Sham group (n = 16)	Group *P* value	Time *P* value	Group x Time *P* value	Within-group effect size g (95% CI)		Between-group effect size g (95% CI)
						Active intervention group	Sham group	Active intervention group vs Sham group
NPRS (chronic back pain one-week average)			0.86	**< 0.001**	0.49			
Pre	5.00 (5.00–7.00)	6.00 (5.38-7.00)						
Post	3.00 (2.25-4.00)	4.00 (3.00–5.00)				**-1.14 (-1.93, -0.34)****	**-1.40 (-2.18, -0.61)*****	-0.37 (-1.32, 0.17)
One-month follow-up	3.00 (2.25-4.00)	4.00 (3.00–5.00)				**-1.01 (-1.80, -0.23)****	**-1.28 (-2.05, -0.50)****	-0.37 (-1.30, 0.19)
Three-month follow-up	4.00 (2.00–5.00)	5.00 (4.00-5.50)				**-1.11 (-1.92, -0.30)****	**-0.85 (-1.58, -0.11)***	-0.24 (-1.22, 0.28)
NPRS (chronic back pain currently)			0.56	**< 0.001**	0.48			
Pre	5.00 (4.25-6.00)	6.00 (5.00-6.62)						
Post	3.00 (2.00–3.00)	4.00 (2.50-4.00)				**-1.22 (-2.02, -0.41)****	**-1.54 (-2.34, -0.74)*****	-0.40 (-1.40, 0.09)
One-month follow-up	3.00 (2.25-3.00)	4.00 (3.00–5.00)				**-1.03 (-1.82, -0.24)***	**-1.10 (-1.85, -0.34)****	-0.43 (-1.37, 0.12)
Three-month follow-up	3.00 (2.00–5.00)	5.00 (2.50–5.50)				**-1.00 (-1.80, -0.20)***	**-0.94 (-1.69, -0.20)***	-0.17 (-1.05, 0.45)
NPRS (chronic knee pain one-week average)			0.84	0.18	0.80			
Pre	5.00 (4.50–5.25)	5.00 (3.50-5.00)						
Post	4.00 (2.75-4.00)	3.50 (3.00–4.00)				-0.86 (-1.88, 0.17)	-0.80 (-1.93, 0.34)	0.02 (-1.01, 1.11)

Outcome measures	Active group (n = 14)	Sham group (n = 16)	Group *P* value	Time *P* value	Group x Time *P* value	Within-group effect size g (95% CI)		Between-group effect size g (95% CI)
						Active intervention group	Sham group	Active intervention group vs Sham group
One-month follow-up	4.00 (2.75-4.00)	3.75 (2.38-4.00)				-0.86 (-1.88, 0.17)	-0.75 (-1.88, 0.38)	0.11 (-0.82, 1.30)
Three-month follow-up	3.00 (2.50–4.50)	4.00 (3.25-4.00)				-0.67 (-1.72, 0.37)	-0.67 (-1.79, 0.45)	0.25 (-0.76, 1.44)
NPRS (chronic knee pain currently)			0.87	0.06	0.58			
Pre	4.50 (3.75–5.25)	5.00 (3.50-5.00)						
Post	3.50 (2.75-4.00)	3.00 (3.00–3.00)				-0.58 (-1.58, 0.42)	-1.38 (-2.58, -0.16)	0.10 (-0.72, 1.41)
One-month follow-up	3.00 (2.75–3.25)	2.50 (2.00-3.75)				-0.82 (-1.84, 0.20)	-1.35 (-2.55, -0.14)	0.13 (-0.78, 1.35)
Three-month follow-up	3.00 (2.50-4.00)	3.50 (2.25-4.00)				-0.47 (-1.50, 0.56)	-0.82 (-1.96, 0.31)	0.32 (-0.66, 1.55)
PSQI			1.00	**< 0.001**	0.17			
Pre	7.50 (5.25–9.50)	10.50 (8.25-15.00)						
Post	15.50 (9.50–19.50)	15.50 (11.00-19.50)				**1.16 (0.36, 1.96)***	0.10 (-0.62, 0.82)	0.30 (-0.45, 1.04)
One-month follow-up	11.50 (6.75–19.25)	17.00 (11.50–21.50)				0.75 (-0.02, 1.51)	0.35 (-0.36, 1.05)	-0.07 (-0.80, 0.65)
Three-month follow-up	13.00 (6.00–19.00)	16.00 (11.00–18.00)				0.72 (-0.06, 1.50)	0.47 (-0.24, 1.19)	-0.09 (-0.86, 0.62)
RMDQ			0.68	0.12	0.33			
Pre	8.00 (4.50–13.00)	8.50 (5.00-13.25)						
Post	5.50 (4.25–8.50)	7.00 (4.50–12.00)				-0.53 (-1.29, 0.22)	-0.20 (-0.91, 0.51)	-0.22 (-0.93, 0.53)

Outcome measures	Active group (n = 14)	Sham group (n = 16)	Group *P* value	Time *P* value	Group x Time *P* value	Within-group effect size g (95% CI)		Between-group effect size g (95% CI)
						Active intervention group	Sham group	Active intervention group vs Sham group
One-month follow-up	4.50 (3.25–7.75)	7.00 (4.00–11.00)				-0.46 (-1.21, 0.29)	-0.15 (-0.86, 0.55)	-0.06 (-0.80, 0.66)
Three-month follow-up	10.00 (4.00–11.00)	10.00 (4.00–13.00)				-0.07 (-0.82, 0.69)	-0.24 (-0.95, 0.47)	0.31 (-0.48, 1.02)
PCS			0.16	0.62	0.34			
Pre	19.00 (9.00-30.50)	21.50 (16.50-35.75)						
Post	20.50 (8.75-24.00)	24.00 (15.00–31.00)				-0.02 (-0.76, 0.72)	-0.14 (-0.84, 0.57)	-3.55 (-1.05, 0.42)
One-month follow-up	14.50 (7.50-21.75)	27.00 (24.50–33.00)				-0.27 (-1.01, 0.48)	0.09 (-0.62, 0.79)	-9.58 (-1.53, -0.02)
Three-month follow-up	18.00 (8.00–30.00)	25.00 (15.50–32.00)				-0.04 (-0.80, 0.71)	-0.05 (-0.75, 0.66)	-4.88 (-1.09, 0.41)
WOMAC total score			0.49	**0.04**	0.86			
Pre	36.50 (25.25–55.50)	30.00 (15.00-40.50)						
Post	18.50 (13.00–40.00)	15.00 (12.75–23.25)				-0.72 (-1.73, 0.29)	-0.60 (-1.72, 0.51)	0.29 (-0.59, 1.56)
One-month follow-up	13.00 (10.50–31.50)	13.00 (8.75–27.75)				-0.97 (-2.01, 0.06)	-0.78 (-1.91, 0.35)	0.46 (-0.62, 1.52)
Three-month follow-up	25.00 (20.00–59.00)	27.00 (20.00–34.00)				-0.31 (-1.33, 0.71)	-0.38 (-1.48, 0.72)	0.65 (-0.65, 1.55)
WOMAC pain subscore			0.62	0.06	0.84			
Pre	9.00 (5.75–12.25)	7.00 (5.00–9.00)						
Post	4.50 (4.00-9.25)	4.50 (4.00-7.25)				-0.57 (-1.57, 0.43)	-0.56 (-1.68, 0.55)	0.12 (-0.82, 1.31)
One-month follow-up	5.00 (3.50–8.25)	3.50 (3.00-7.75)				-0.66 (-1.66, 0.35)	-0.73 (-1.85, 0.40)	0.32 (-0.68, 1.46)

Outcome measures	Active group (n = 14)	Sham group (n = 16)	Group *P* value	Time *P* value	Group x Time *P* value	Within-group effect size g (95% CI)		Between-group effect size g (95% CI)
						Active intervention group	Sham group	Active intervention group vs Sham group
Three-month follow-up	7.00 (5.00-13.50)	8.00 (4.75-9.00)				-0.15 (-1.17, 0.87)	-0.32 (-1.41, 0.78)	0.34 (-0.72, 1.48)
WOMAC stiffness subscore			0.81	0.05	0.86			
Pre	3.50 (1.50–5.25)	2.00 (1.00–4.00)						
Post	2.00 (0.75–2.50)	2.50 (0.50-3.00)				-0.31 (-1.30, 0.68)	-0.27 (-1.36, 0.83)	0.07 (-0.99, 1.13)
One-month follow-up	0.50 (0.00–2.00)	1.50 (0.25–2.75)				-0.72 (-1.73, 0.29)	-0.47 (-1.57, 0.64)	-0.22 (-1.27, 0.85)
Three-month follow-up	2.00 (1.00-4.50)	2.50 (1.25–3.75)				-0.18 (-1.20, 0.84)	-0.02 (-1.11, 1.07)	-0.06 (-1.15, 1.04)
WOMAC physical function subscore			0.33	**0.009**	0.99			
Pre	26.00 (17.00–38.00)	14.00 (9.50–29.50)						
Post	12.00 (9.75–28.75)	10.00 (7.25–12.75)				-0.75 (-1.76, 0.27)	-0.57 (-1.68, 0.55)	0.38 (-0.48, 1.68)
One-month follow-up	9.00 (6.75–21.25)	8.50 (5.00–18.00)				-1.00 (-2.04, 0.04)	-0.71 (-1.83, 0.42)	0.46 (-0.59, 1.56)
Three-month follow-up	17.00 (13.50–41.00)	19.50 (10.00-22.25)				-0.31 (-1.33, 0.71)	-0.27 (-1.36, 0.83)	0.51 (-0.64, 1.57)

3.3. Executive function performance

No significant group-by-time interactions were found for cognitive tasks. In the Stroop Task, a significant main effect of time was observed in the reduction of number of errors on incongruent trials post-treatment ($P < 0.05$). Specifically, within the sham group, post-treatment performance showed an error reduction trend ($P_{FDR-corrected} = 0.01$). No statistically significant main effect of time or group differences was found in the More-Odd-Shifting Task and 2-back Task (Table 3).

Table 3
Medians, interquartile range, and effect sizes for cognitive performance.

Outcome measures	Active group (n = 14)	Sham group (n = 16)	Group *P* value	Time *P* value	Group x Time *P* value	Within-group effect size g (95% CI)		Between-group effect size g (95% CI)
						Active intervention group	Sham group	Active intervention group vs Sham group
Color-Word Matching Stroop Task								
Congruent ACC, %			0.91	0.78	0.87			
Pre	99.00% (97.00-100.00%)	97.00% (95.00-100.00%)						
Post	100.00% (100.00-100.00%)	100.00% (100.00-100.00%)				0.33 (-0.07, 0.73)	0.91 (0.47, 1.36)	-0.16 (-0.93, 0.60)
Congruent RT, median (IQR)			0.84	0.84	0.84			
Pre	843.34 (759.36-935.45)	815.48 (712.03-869.13)						
Post	882.78 (767.20-937.96)	827.32 (768.67-950.78)				-0.05 (-0.43, 0.34)	0.44 (0.05, 0.83)	0.04 (-0.72, 0.80)
Incongruent ACC, %			0.96	0.07	0.49			
Pre	95.00% (46.00%-97.00%)	91.00% (20.00–98.00%)						
Post	97.00% (93.00–98.00%)	98.00% (97.00-100.00%)				0.59 (0.17, 1.01)	0.78 (0.36, 1.21)	-0.72 (-1.50, 0.07)
Incongruent RT, median (IQR)			0.84	0.63	0.84			
Pre	1034.91 (947.71-1115.07)	864.21 (779.00-991.68)						
Post	1055.33 (930.89-1144.22)	971.32 (881.99-1113.53)				-0.04 (-0.43, 0.34)	0.67 (0.25, 1.08)	0.21 (-0.55, 0.98)
Interference effect [ACC difference			0.93	0.40	0.84			

between conditions, %]								
Pre	3.00% (2.00–13.00%)	7.00% (1.00–75.00%)						
Post	2.00% (2.00–7.00%)	0.00% (0.00–2.00%)				-0.23 (-0.62, 0.17)	-0.79 (-1.24, -0.35)	0.68 (-0.12, 1.48)
Interference effect [Time difference between conditions, median (IQR)]			0.84	0.84	0.93			
Pre	169.91 (120.93-213.84)	100.02 (51.07-155.31)						
Post	166.47 (106.49-215.69)	142.63 (101.83-169.44)				-0.01 (-0.40, 0.38)	0.39 (0.005, 0.78)	0.47 (-0.30, 1.25)
The number of errors on incongruent trials, median (IQR)			0.97	**0.02***	0.84			
Pre	3.00 (2.00-31.25)	5.50 (1.00-47.25)						
Post	1.50 (1.00–4.00)	1.00 (0.00-1.50)				-0.62 (-1.05, -0.20)	**-1.05 (-1.52, -0.58)***	0.72 (-0.07, 1.51)
Congruent residual ISD, median (IQR)			0.84	1.00	0.93			
Pre	10.55 (8.78–12.27)	8.50 (7.24–10.02)						
Post	10.15 (8.93–11.84)	8.93 (7.16–11.16)				-0.21 (-0.60, 0.18)	0.12 (-0.26, 0.49)	0.15 (-0.61, 0.92)
Congruent raw ISD, median (IQR)			0.84	0.84	0.96			
Pre	216.80 (182.05-249.55)	183.70 (146.78-207.78)						
Post	228.75 (195.30-254.72)	198.60 (167.20-255.75)				0.04 (-0.35, 0.43)	0.27 (-0.11, 0.65)	0.15 (-0.62, 0.91)

Congruent intraindividual coefficient of variation, median (IQR)			0.84	0.97	1.00			
Pre	0.25 (0.23–0.29)	0.23 (0.21–0.26)						
Post	0.25 (0.21–0.31)	0.23 (0.20–0.28)				0.001 (-0.39, 0.39)	0.07 (-0.30, 0.45)	0.25 (-0.52, 1.02)
Incongruent residual ISD, median (IQR)			0.84	1.00	0.85			
Pre	10.73 (9.20-11.95)	8.11 (7.33–10.11)						
Post	9.73 (8.58–10.50)	9.96 (8.34–11.31)				-0.28 (-0.67, 0.12)	0.16 (-0.22, 0.53)	0.03 (-0.73, 0.80)
Incongruent raw ISD, median (IQR)			0.84	0.84	0.88			
Pre	288.90 (248.40-318.95)	222.00 (203.05-278.57)						
Post	243.75 (216.53-276.83)	246.20 (207.35–289.50)				-0.69 (-1.12, -0.26)	-0.06 (-0.43, 0.31)	0.02 (-0.75, 0.78)
Incongruent intraindividual coefficient of variation, median (IQR)			0.97	0.63	0.93			
Pre	0.28 (0.25–0.29)	0.26 (0.22–0.30)						
Post	0.24 (0.22–0.27)	0.25 (0.23–0.28)				-0.62 (-1.04, -0.20)	-0.29 (-0.67, 0.09)	-0.24 (-1.01, 0.52)
More-Odd-Shifting Task								
Block AB, ACC, %			0.88	1.00	0.84			
Pre	93.00% (88.00–96.00%)	97.00% (93.00–98.00%)						
Post	94.00% (91.00–96.00%)	97.00% (91.00–97.00%)				0.17 (-0.22, 0.57)	-0.09 (-0.46, 0.29)	-0.30 (-1.08, 0.48)
Block AB, RT, median (IQR)			0.93	0.84	0.78			

Pre	916.61 (813.42-969.79)	851.59 (780.39-902.91)						
Post	837.47 (750.19-880.06)	873.95 (784.43-925.91)				-0.52 (-0.94, -0.11)	0.22 (-0.16, 0.59)	-0.37 (-1.15, 0.41)
Block C, ACC, %			1.00	0.21	0.72			
Pre	85.00% (73.00–89.00%)	86.00% (76.00–91.00%)						
Post	87.00% (72.00–93.00%)	91.00% (88.00–96.00%)				0.19 (-0.21, 0.58)	**1.05 (0.59, 1.52)***	-0.67 (-1.47, 0.13)
Block C, RT, median (IQR)			0.85	0.89	0.85			
Pre	1247.61 (1063.29-1313.02)	1255.93 (1137.07-1307.99)						
Post	1146.77 (982.68-1201.75)	1193.59 (1128.18-1340.01)				-0.31 (-0.71, 0.09)	-0.02 (-0.39, 0.35)	-0.67 (-1.47, 0.13)
Global cost, ACC difference, %			0.97	0.63	0.78			
Pre	10.00% (2.00–14.00%)	10.00% (6.00–19.00%)						
Post	4.00% (2.00–11.00%)	2.00% (1.00–7.00%)				-0.18 (-0.60, 0.25)	-0.73 (-1.18, -0.27)	0.30 (-0.52, 1.11)
Global cost, RT, median (IQR)			0.96	0.97	1.00			
Pre	320.48 (240.88–404.90)	360.72 (232.11–465.60)						
Post	324.67 (255.77-409.51)	292.48 (266.71-381.01)				-0.06 (-0.45, 0.32)	-0.16 (-0.54, 0.22)	-0.39 (-1.18, 0.39)
Local cost, ACC difference, %			0.97	0.84	0.84			
Pre	7.00% (5.00–13.00%)	8.00% (0.00–15.00%)						
Post	11.00% (7.00–15.00%)	7.00% (5.00–9.00%)				0.33 (-0.11, 0.76)	0.08 (-0.39, 0.55)	0.57 (-0.26, 1.40)
Local cost, RT, median			0.85	0.88	0.74			

(IQR)								
Pre	86.20 (28.62-175.62)	83.05 (13.84-140.04)						
Post	88.41 (-13.93-136.49)	167.48 (87.71-197.67)				-0.19 (-0.58, 0.20)	0.40 (0.01, 0.79)	-0.58 (-1.37, 0.22)
Block AB, residual ISD, median (IQR)			0.84	0.97	0.96			
Pre	9.61 (8.01–11.23)	9.63 (8.27–11.51)						
Post	9.71 (8.10-11.43)	10.13 (8.04–11.22)				-0.06 (-0.45, 0.33)	0.04 (-0.33, 0.42)	-0.23 (-1.01, 0.55)
Block AB, raw ISD, median (IQR)			0.84	0.84	0.99			
Pre	232.00 (208.50-281.38)	244.15 (206.03-298.77)						
Post	239.65 (198.68-285.45)	246.00 (200.85–275.50)				-0.17 (-0.57, 0.22)	-0.17 (-0.54, 0.21)	-0.17 (-0.95, 0.60)
Block AB, intraindividual coefficient of variation, median (IQR)			0.84	0.84	0.85			
Pre	0.27 (0.25–0.32)	0.28 (0.27–0.33)						
Post	0.29 (0.24–0.34)	0.29 (0.25–0.31)				0.10 (-0.29, 0.49)	-0.32 (-0.70, 0.07)	0.09 (-0.68, 0.87)
Block C, residual ISD, median (IQR)			0.84	1.00	0.97			
Pre	9.99 (9.02–10.61)	10.19 (9.30-11.04)						
Post	9.44 (9.18–10.70)	10.44 (9.63–10.80)				0.09 (-0.30, 0.47)	-0.09 (-0.46, 0.29)	-0.43 (-1.22, 0.35)
Block C, raw ISD, median (IQR)			0.84	0.85	0.97			
Pre	297.05 (262.23-319.73)	300.85 (277.15-331.85)						

Post	275.00 (263.50-307.03)	299.10 (277.65-308.25)				-0.05 (-0.43, 0.34)	-0.33 (-0.71, 0.05)	-0.42 (-1.21, 0.36)
Block C, intraindividual coefficient of variation, median (IQR)			1.00	0.96	0.85			
Pre	0.24 (0.22–0.28)	0.25 (0.23–0.27)						
Post	0.26 (0.24–0.27)	0.25 (0.23–0.26)				0.15 (-0.24, 0.54)	-0.27 (-0.65, 0.11)	0.30 (-0.49, 1.08)
Digit 2-back Task, ACC, %			0.88	0.91	1.00			
Pre	88.14% (67.30-93.33%)	93.74% (87.13–95.09%)						
Post	86.00% (74.00–96.00%)	92.00% (82.00–96.00%)				-0.07 (-0.46, 0.32)	0.008 (-0.37, 0.38)	-0.30 (-1.18, 0.58)
Digit 2-back Task, RT, median (IQR)			0.96	0.84	0.84			
Pre	838.41 (799.28-1046.72)	995.77 (842.15-1150.67)						
Post	961.64 (885.71-1126.03)	962.34 (872.53-1086.33)				0.32 (-0.08, 0.71)	-0.30 (-0.69, 0.08)	-0.30 (-1.18, 0.58)
Digit 2-back Task, residual ISD, median (IQR)			1.00	0.96	0.84			
Pre	9.48 (8.81–10.50)	9.94 (9.21–11.22)						
Post	10.58 (8.48–11.31)	9.58 (8.34–12.33)				0.22 (-0.17, 0.61)	-0.17 (-0.55, 0.20)	0.19 (-0.69, 1.06)
Digit 2-back Task, raw ISD, median (IQR)			1.00	0.97	0.84			
Pre	257.85 (239.40-286.52)	270.15 (250.23-305.18)						
Post	296.40 (237.15-315.15)	270.30 (234.40-344.65)				0.33 (-0.07, 0.73)	-0.04 (-0.42, 0.33)	0.18 (-0.70, 1.05)
Digit 2-back Task,			0.93	0.84	1.00			

intraindividual coefficient of variation, median (IQR)					
Pre	0.28 (0.24–0.31)	0.26 (0.24–0.32)			
Post	0.28 (0.27–0.31)	0.29 (0.26–0.33)	0.15 (-0.24, 0.54)	0.16 (-0.22, 0.54)	0.16 (-0.72, 1.03)

3.4. Functional magnetic resonance imaging outcomes

After exclusion of data due to excessive head motion or poor task performance (Stroop Task n = 3; More-Odd-Shifting Task n = 4; 2-back Task n = 5), there were no significant group-by-time interaction or main effects of time or group on neural activity during the Stroop and 2-back tasks (all $P > 0.05$). For the More-Odd-Shifting task (mixed-task > single-task), neither the group-by-time interaction nor the main effect of time reached significance. However, a significant main effect of group was observed ($P_{FDR-corrected} = 0.03$), with the active group exhibiting higher overall neural activation in the left inferior and superior parietal lobules than the sham group across two timepoints. For the More-Odd-Shifting Task [switch-versus-repeat contrast for the within mixed-task blocks], a significant group-by-time interaction was observed in the activity of the left inferior parietal lobule ($P_{FDR-corrected} = 0.001$) and the left superior parietal lobule ($P_{FDR-corrected} = 0.003$). Post-hoc analyses revealed that while the active group had significantly lower baseline activation than the sham group ($P_{FDR-corrected} < 0.05$), this difference was non-significant post-treatment ($P > 0.05$). This interaction was driven by a significant post-treatment reduction in activation of both regions within the sham group ($P_{FDR-corrected}=0.002$), while activation in the active group remained stable ($P > 0.05$) (Fig. 4).

3.5. Sensitivity analysis

The sensitivity analysis confirmed the robustness of the primary findings (Table S5).

3.6. Qualitative assessments

Semi-structured interviews (n = 10) revealed divergent experiences. Regarding perceived changes, four participants (40%) reported cognitive/emotional improvements. Among these four, three (75%) also reported reduced CLBP-related symptoms (rather than CKP) and enhanced mobility. The remaining six (60%) reported no obvious changes in various domains (chronic pain, sleep quality, or cognitive function). Barriers to participation included scheduling conflicts, cognitive task difficulty, and discomfort during iTBS or MRI procedures. Four participants highly praised the supportive staff as a facilitator to participation. Participants suggested shortening treatment session durations, enhancing comfort by reducing iTBS head coil's pressure, increasing treatment intensity, and providing clearer task instructions to improve future trial utility (Supplementary Results 1).

4. Discussion

This pilot RCT demonstrates that all progression metrics successfully met the "Green (Go)" criteria, revealing that a 12-session L-DLPFC-iTBS protocol is feasible, safe, and highly acceptable for older adults with CMP. While both active and sham groups exhibited reductions in CLBP intensity, these improvements did not reach the MCID. Unexpectedly, active stimulation was associated with a mild, subclinical decline in sleep quality. Conversely, the sham group produced a slight improvement in executive function. The task-specific modulation of frontoparietal activity during the cognitive switching task suggests that L-DLPFC-iTBS influences the neural substrates of executive control. Qualitative insights revealed perceived cognitive and pain-related benefits from participants, barriers, and suggestions for future studies. These findings support the implementation of a definitive, adequately powered RCT.

The trial's viability was confirmed by a completion rate (93.3%) that exceeds median reported for similar neuromodulation research.[65] Importantly, despite the rigorous logistics required to coordinate brain stimulation sessions and the highly competitive MRI scheduling environment at PolyU, our protocol achieved a 93.3% completion rate. Our feasibility findings are consistent with those reported in our previous rTMS study targeting individuals with concomitant insomnia and CLBP.[38] The favorable safety profile, characterized by infrequent and minor adverse events (e.g., headache) in both groups, aligns with previous iTBS literature.[16] These findings coupled with high acceptability scores and effective blinding, suggest that the intensive 12-session protocol is acceptable by older adults with CMP. Taken together, achieving the "Green (Go)" status demonstrates that our study's administrative workflow and inter-departmental logistics are fully optimized, safely paving the way for managing a larger cohort in a future definitive RCT.

Our observation that both groups experienced pain reduction sustained through immediately post-treatment and follow-ups without reaching the MCID warrants careful interpretation. The analgesic effect in the sham group may reflect a strong placebo response, a neurobiological phenomenon characterized by reduced pain- and emotion-related brain activity alongside enhanced fronto-striatal-brainstem circuit engagement.[66] The lack of a superior effect in the active group may be attributed to the small sample size or the "aging brain" hypothesis: cortical atrophy, reduced hemispheric asymmetry, and white matter lesions disrupt signal propagation.[67] Additionally, shifted Gamma-Aminobutyric Acid-mediated intracortical inhibition over glutamatergic activity,[68] together with a decline in cortical plasticity may require higher stimulation intensities or more frequent sessions to induce stable long-term potentiation.[69] Further, the limited number of treatment sessions and the absence of concurrent exercise therapy may have limited the overall clinical effect compared to previous research.[16]

The significant deterioration in sleep quality within the active group at one month is a novel, albeit subclinical finding. The change did not meet the MCID for the PSQI (≥ 2.5 points), suggesting only a mild subjective disturbance.[70] While previous RCTs using inhibitory paradigms (e.g., low-frequency rTMS) have reported significant improvements in sleep parameters,[38, 71] high-frequency rTMS (such as iTBS) promotes cortical excitability. This may contribute to hyperarousal processes and the disruption of sleep homeostasis.[72]

The executive function results were paradoxical, as significant executive function improvement (fewer response inhibition errors) appeared to be confined to the sham group. Research illustrated that the post-stimulation brain might enter a transient perturbation phase, where active iTBS induces a transient state of neural reorganization that obscures immediate performance gains.[73] Substantive and lasting improvements typically manifest only after the reorganization process reaches its culmination.[74] Conversely, the sham group improvement likely reflects a pure practice effect immediately post-intervention.

Our fMRI results revealed iTBS-induced neuroplastic changes exclusively during the More-Odd-Shifting Task. In the task-switching paradigm, the active group demonstrated higher parietal activation during the mixed-task cost (mixed > single) than the sham group at both pre- and post-treatment timepoints. This suggests that iTBS enhanced the sustained engagement of frontoparietal regions necessary for maintaining stable and multiple task sets.[75] Conversely, the switch cost (switch > repeat) followed a different pattern. While the sham group showed a decrease in neural activity over time, the active group maintained stable, low-level neural activation. This implies that iTBS may modulate frontoparietal dynamics to prevent further practice-induced downregulation, whereas the reductions observed in the sham group may reflect standard practice effects.[76]

Qualitative findings provided valuable user-centered perspectives that quantitative scales often overlook, particularly regarding the lived experience of the intervention. While participants valued the supportive research environment, their feedback highlighted specific logistical and ergonomic challenges (e.g., scheduling conflicts, physical pressure of the head coil). The perceived complexity of the fMRI tasks underscores the risk of participant burden during neuroimaging, which may reduce adherence and data quality.[77] These insights suggest that future definitive RCTs should prioritize

ergonomic coil positioning and consider “gamified” or abbreviated cognitive tasks to maintain engagement and data quality in older populations.

Our study is characterized by several methodological strengths. First, we utilized individualized structural MRI for navigation, allowing for more precise targeting compared to the use of standard head models inside the rTMS navigation system.[78] Second, we employed a sham TMS coil in combination with electrical stimulation for blinding, which mimics the auditory effects of active TMS without actual stimulation of the brain.[34] Third, our blinded evaluation confirmed that blinding was largely maintained.

However, our study has limitations inherent to its pilot design. First, the small sample size was underpowered for formal hypothesis testing of clinical efficacy and iTBS-related neural changes. Second, the inclusion of participants with both isolated CLBP and comorbid CKP introduced clinical heterogeneity, which may have diluted site-specific effects. Third, while our stimulation protocol adhered to an established guideline,[30] it remains unclear whether our dosage is optimal for older adults with CMP.

5. Conclusions

By successfully satisfying all pre-specified “Green (Go)” feasibility criteria, this pilot trial demonstrates that L-DLPFC-iTBS is a feasible, safe, and well-tolerated treatment for older adults with CLBP and comorbid CKP. The intervention may induce task-specific modulation of neural activity during cognitive switching, suggesting a potential central mechanism by which iTBS may influence pain perception. By optimizing the dosage, refining the sham-control to account for practice effects, and addressing barriers identified by our participants, a large-scale RCT is fully cleared to proceed and will be well-positioned to further elucidate the neuromodulatory effects of iTBS on the cognitive-effective dimensions of chronic pain in older adults.

Abbreviations

CKP
Chronic knee pain
CLBP
Chronic low back pain
CMP
Chronic musculoskeletal pain
CONSORT
Consolidated Standards of Reporting Trials
DLPFC
Dorsolateral prefrontal cortex
FDR
False discovery rate
fMRI
Functional magnetic resonance imaging
FRAIL
Fatigue, Resistance, Ambulation, Illness, and Loss
iTBS
Intermittent theta burst stimulation
L-DLPFC
Left dorsolateral prefrontal cortex
L-DLPFC-iTBS

Intermittent theta burst stimulation targeting the left dorsolateral prefrontal cortex
MCID
Minimal clinically important difference
MRI
Magnetic resonance imaging
NIBS
Non-invasive brain stimulation
NPRS
Numerical pain rating scale
PolyU
The Hong Kong Polytechnic University
PSQI
Pittsburgh Sleep Quality Index
RCT
Randomized controlled trial
RMDQ-HK
Hong Kong Chinese Version of the Roland-Morris Disability Questionnaire
rTMS
Repetitive transcranial magnetic stimulation
SPM12
Statistical Parametric Mapping 12
TMS
Transcranial magnetic stimulation

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (HSEARS20240411013) of The Hong Kong Polytechnic University, registered at *ClinicalTrials.gov* (NCT06709963).

Consent for publication

Not applicable.

Competing Interests

Frank F Huang: Conceptualization, Methodology, Formal analysis, Writing-original draft preparation. Tony SH Chiu: Data curation, Methodology. Chuhuai Wang: Resources, Project administration. Tommy LH Lam: Supervision, Project administration, Writing-review & editing. Jiajia Yang: Conceptualization, Supervision, Writing-review & editing. Alexander T Sack: Writing- review & editing. Chun Liang Hsu: Writing- review & editing. Janet Lok Chun Lee: Conceptualization, Software, Supervision, Writing-review & editing. Jeremy R Chang: Writing-review & editing. Daniel KY Zheng: Writing-review & editing. Fadi M Al Zoubi: Writing-review & editing. Siu-Ngor Fu: Project administration. Arnold YL Wong: Conceptualization, Project administration, Writing-review & editing.

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Author Contribution

Frank F Huang: Conceptualization, Methodology, Formal analysis, Writing-original draft preparation. Tony SH Chiu: Data curation, Methodology. Chuhuai Wang: Resources, Project administration. Tommy LH Lam: Supervision, Project administration, Writing-review & editing. Jiajia Yang: Conceptualization, Supervision, Writing-review & editing. Alexander T Sack: Writing- review & editing. Chun Liang Hsu: Writing- review & editing. Janet Lok Chun Lee: Conceptualization, Software, Supervision, Writing-review & editing. Jeremy R Chang: Writing-review & editing. Daniel KY Zheng: Writing-review & editing. Fadi M Al Zoubi: Writing-review & editing. Siu-Ngor Fu: Project administration. Arnold YL Wong: Conceptualization, Project administration, Writing-review & editing.

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Availability of data and materials

The corresponding author had full access to all study data and assumed final responsibility for the decision to submit the work for publication. All data and program codes are available on request.

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Figures

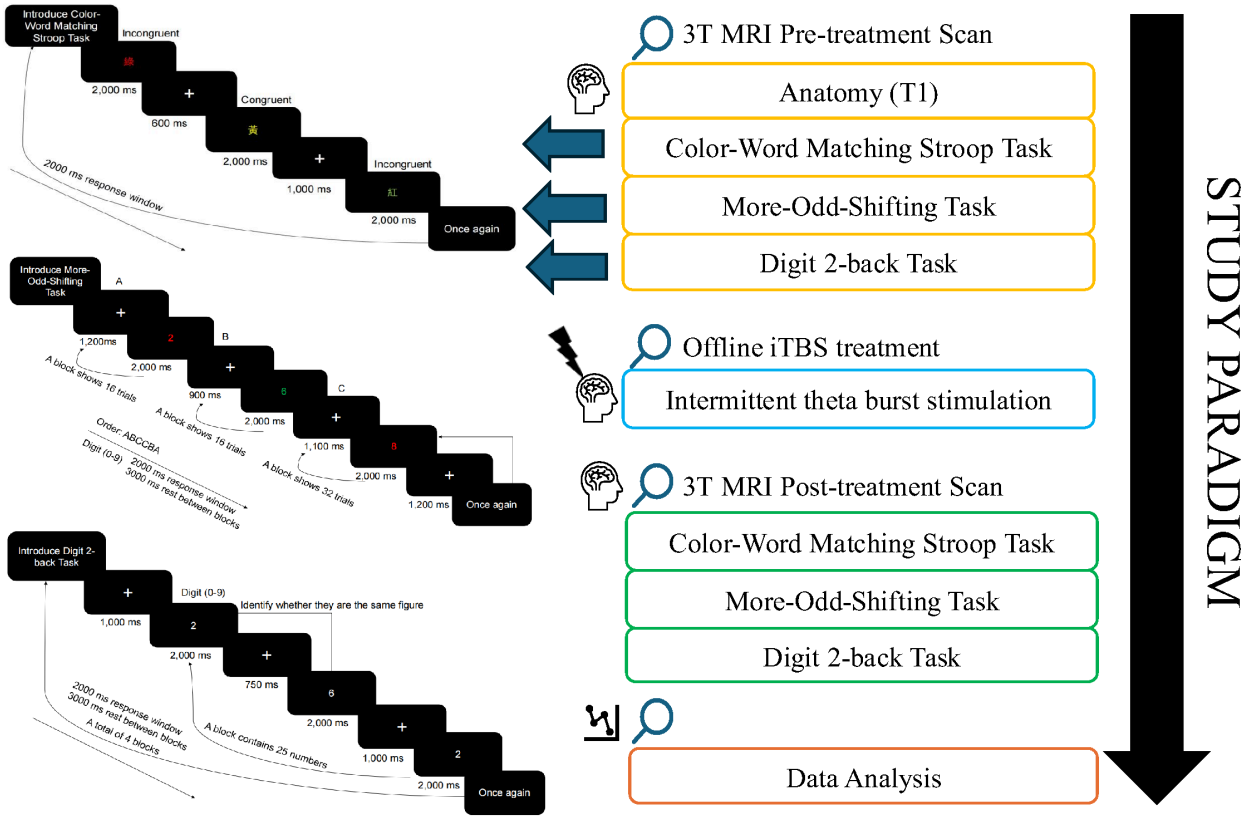
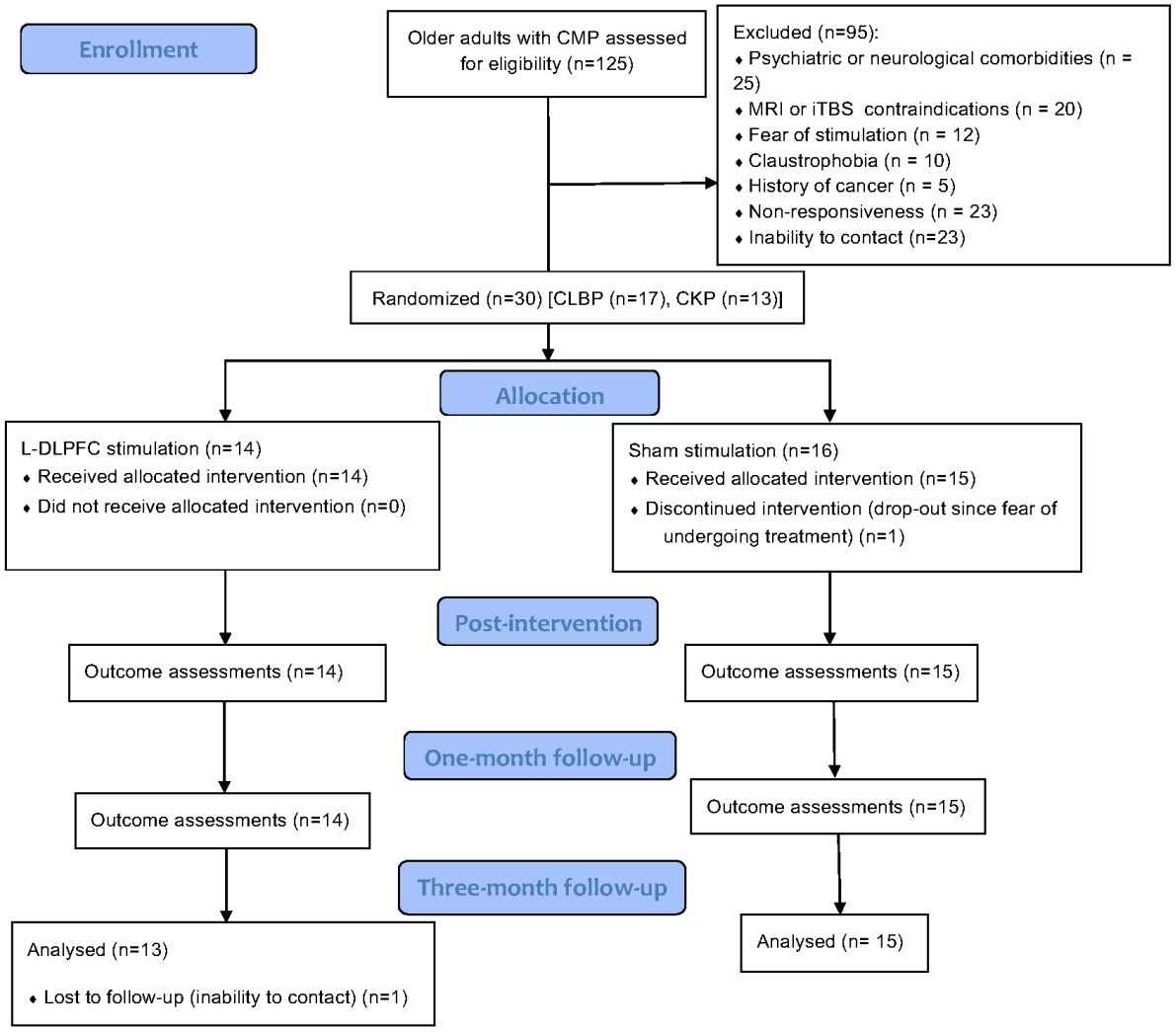


Figure 1

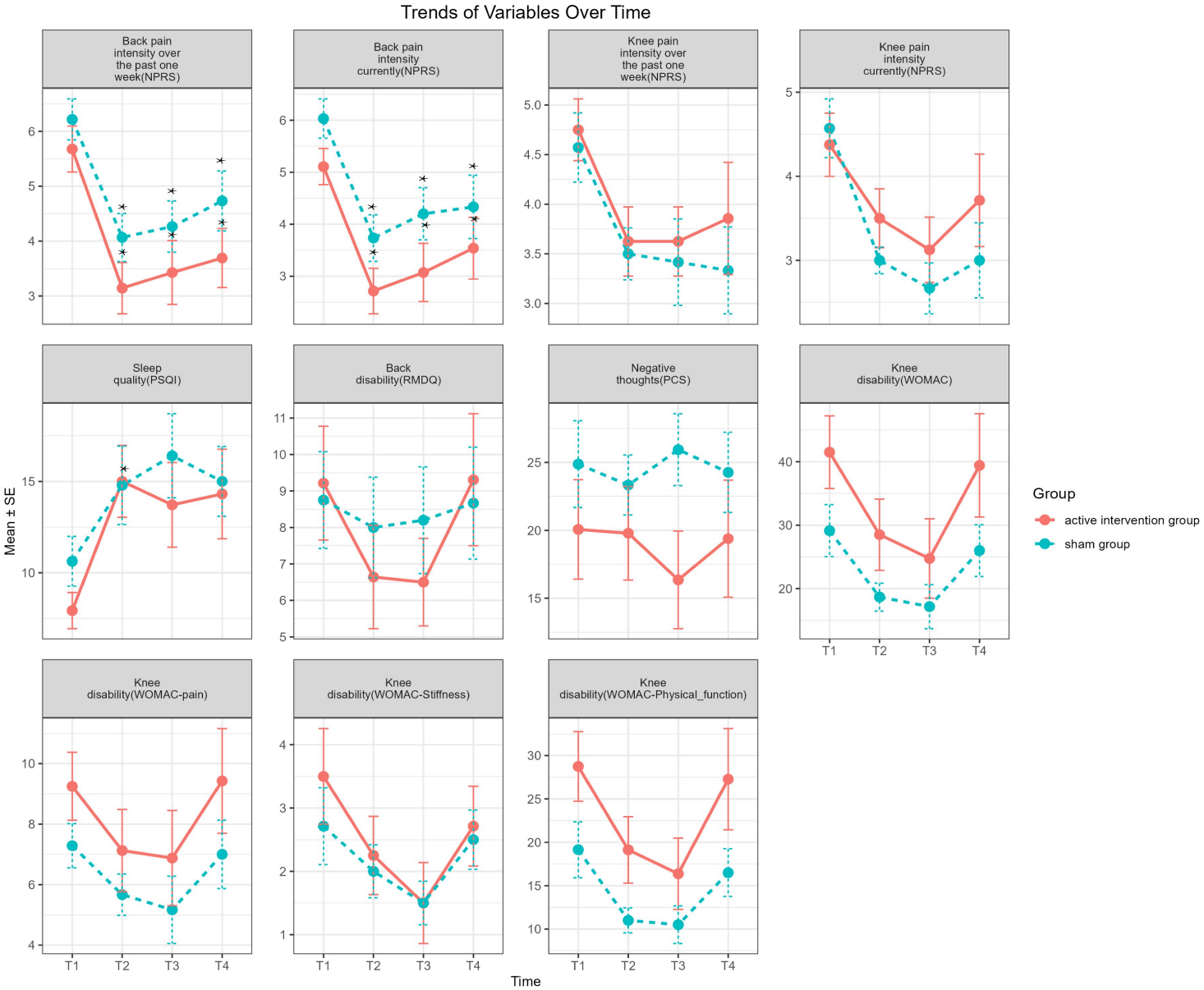
Study Procedure.



Abbreviations: CMP, chronic musculoskeletal pain; CLBP, chronic low back pain; CKP, chronic knee pain; iTBS, intermittent theta burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex.

Figure 2

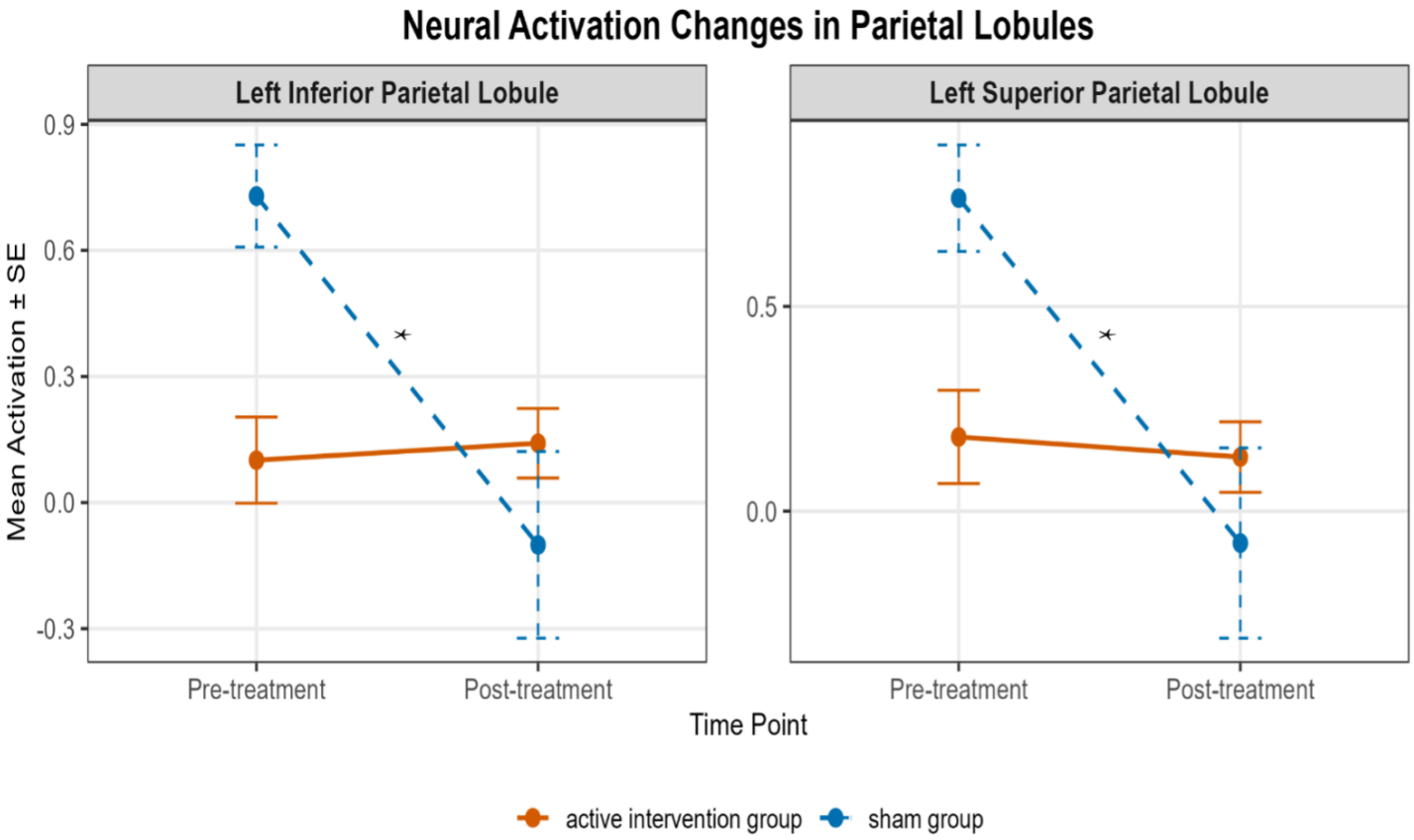
A CONSORT flow diagram of the study.



Notes: T1: pre-treatment; T2: post-treatment; T3: one-month follow-up; T4: three-month follow-up; Values are presented as mean and standard error; *: a significant difference between active intervention and sham group;
Abbreviation: NPRS, Numerical Pain Rating Scale; PSQI, Pittsburgh Sleep Quality Index; RMDQ, Roland-Morris Disability Questionnaire; PCS, Pain Catastrophizing Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 3

Patient-reported outcome measures.



Notes: Values are presented as mean and standard error; *: a significant difference.

Figure 4

Functional magnetic resonance imaging outcomes of More-Odd-Shifting task.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx