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Double-Cone-Coil iTBS for Poststroke Lower-Limb Recovery: A Randomized Sham-Controlled Trial with Treatment-Informed Response Prediction

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***Abstract*—Lower-limb impairment after stroke limits walking independence and participation, and the deep and medial location of the lower-limb motor representation poses practical challenges for noninvasive cortical stimulation. We investigated whether double-cone-coil intermittent theta-burst stimulation (iTBS) added to conventional rehabilitation could enhance poststroke lower-limb recovery, with treatment-informed response prediction as a secondary analysis. In this single-center, randomized, sham-controlled trial, 48 adults 3–12 months after a first unilateral stroke were assigned 1:1 to active iTBS or sham stimulation. Participants and outcome assessors were blinded to treatment allocation. Both groups received conventional rehabilitation for 6 weeks, with active or sham stimulation delivered over the affected lower-limb motor representation for 15 sessions. The primary outcome was 10-m walk test (10MWT) gait speed. Week 3, immediately after the stimulation course, was the principal clinical comparison, and Week 6 assessed the between-group difference during continued rehabilitation. Active iTBS improved 10MWT speed versus sham at Week 3 (adjusted difference, 0.112 m/s; 95% CI, 0.074–0.151; P<0.001), with the between-group advantage remaining evident at Week 6 (0.126 m/s; 95% CI, 0.088–0.165; P<0.001). FMA-LE and Berg Balance Scale outcomes also favored active iTBS at both assessments after multiplicity adjustment. No serious adverse events or adverse event-related discontinuations were recorded. In the secondary prediction analysis, 23 of 46 participants met the defined Week 6 response threshold. A ridge model combining baseline 10MWT, TUGT, FMA-LE, and treatment assignment achieved an internally evaluated AUROC of 0.909 and Brier score of 0.129. These findings support double-cone-coil iTBS as a promising adjunct to poststroke lower-limb rehabilitation and suggest that readily available clinical information, together with treatment received, may help characterize heterogeneity in recovery.**

***Index Terms*—Stroke rehabilitation, intermittent theta-burst stimulation, gait speed, randomized controlled trial, treatment-response prediction.**

I. Introduction

Walking recovery is a central goal of stroke rehabilitation because mobility supports independence, participation, and return to daily activities. Gait speed measured with the 10-m walk test (10MWT) is reproducible and responsive to change after stroke [1, 2]. Speed-based categories provide clinically interpretable benchmarks for household and community ambulation, and transitions between categories are associated with broad functional gains [3, 4]. Gait speed also serves as a continuous measure that can reflect minor improvements and large functional shifts without reducing all changes into a binary category. Recovery, however, is heterogeneous. Patients with similar diagnoses and rehabilitation exposure may exhibit substantial differences in later walking performance, and baseline gait capacity explains only part of that variation [5, 6]. The clinical importance of walking recovery and the substantial variability in recovery highlight the need for effective adjunctive strategies to enhance lower-limb function after stroke.

Noninvasive brain stimulation has emerged as a viable approach. However, applying this approach to the lower-limb motor system poses practical challenges. The leg representation lies deep and medially near the interhemispheric fissure, and stimulation of this region produces descending volleys different from those elicited by stimulation of more superficial hand representations [7]. Tibialis anterior hotspots also vary across individuals and may be altered after a stroke [8]. These anatomical and physiological features make coil selection and target localization important methodological considerations. A double-cone coil can improve access to lower-limb representations, although increased stimulation depth results in reduced focality [9, 10]. Intermittent theta-burst stimulation (iTBS) delivers patterned bursts over a brief session and can

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produce sustained changes in motor cortical excitability [11]. Its brief administration is attractive for rehabilitation processes, although whether these physiological effects translate into functional benefit after stroke requires clinical evaluation. Early gait-focused work supported the clinical feasibility of double-cone-coil stimulation [12]. Lower-limb randomized trials have since reported promising effects with motor cortical or related stimulation protocols, but targets, schedules, comparators, and outcomes exhibit variability [13, 14]. Recent synthesis also suggests potential lower-limb motor and balance benefits while emphasizing limited and variable evidence [15]. These uncertainties support direct randomized evaluation of the specific double-cone-coil iTBS protocol used in this study.

Even when a randomized trial demonstrates an average benefit, substantial interindividual variability in recovery may remain. Baseline walking capacity, integrated mobility, and lower-limb motor impairment describe complementary aspects of rehabilitation status and have been associated with subsequent gait recovery [5, 6]. Lower-extremity motor-evoked potentials (MEPs) and trial-based biomarker analyses further suggest that neurophysiological and clinical measures provide prognostic information but do not fully explain individual recovery pathways [16, 17]. Rehabilitation engineering studies have used multistate neurophysiological information and multimodal behavioral data to predict lower-limb motor gains or treatment responses [18, 19]. PREP2 provides a comprehensive model for combining clinical assessments with biomarker information in recovery prediction [20], but its focus on acute upper-limb recovery differs substantially from the present context. A parsimonious model based on routinely available clinical measures may be easy to reproduce across rehabilitation settings, but it still requires careful evaluation. For observed-response prediction within an RCT, randomized treatment assignment can be incorporated with baseline clinical factors. This analysis can assess whether baseline clinical status contributes predictive information beyond treatment assignment, while remaining distinct from the estimation of individualized treatment effects.

Therefore, we conducted a randomized sham-controlled trial to determine whether double-cone-coil iTBS added to conventional rehabilitation improved poststroke lower-limb recovery, with 10MWT gait speed as the primary clinical outcome [21]. Week 3, immediately after the stimulation course, was the principal clinical comparison, and Week 6 assessed whether the between-group difference persisted during continued rehabilitation. Supportive outcomes assessed lower-limb motor impairment, balance, mobility, and independence. As a secondary extension, a parsimonious ridge model combined baseline 10MWT, Timed Up and Go test, lower-extremity Fugl–Meyer score, and received treatment to estimate threshold-defined Week 6 response. The model used prespecified baseline clinical measures together with received treatment while deliberately limiting model complexity. This design allowed us to evaluate randomized clinical efficacy and explore whether readily available clinical information could help characterize heterogeneity in Week 6 response.

II. Materials and Methods

A. Study Design, Setting, and Participants

This single-center, parallel-group, randomized, sham-controlled trial was conducted at Wuxi Central Rehabilitation Hospital, Wuxi, China. The study was approved by the Medical Ethics Committee of Wuxi Central Rehabilitation Hospital (WXMHCIRB2023LLky078), registered with the Chinese Clinical Trial Registry (ChiCTR2300077431; November 8, 2023), and conducted in accordance with the Declaration of Helsinki. The trial protocol was published previously [21]. All participants provided written informed consent before randomization. Recruitment commenced in May 2024, and follow-up was completed in November 2025.

Eligible participants were 40–80 years of age and experienced a first unilateral stroke with hemiparesis attributable to a left or right subcortical lesion, as confirmed by computed tomography or magnetic resonance imaging, 3–12 months after stroke onset. Participants were required to have Brunnstrom stage III–V lower-limb recovery, be able to walk independently for at least 10 m with or without an orthotic device, and possess sufficient communication and cognitive skills to complete the intervention and outcome assessments. Key exclusion criteria included contraindications to iTBS or MRI, pregnancy, pre-existing lower-limb motor impairment, substantial pain that could interfere with assessment (visual analogue scale >4), severe communication, sensory, cognitive (Mini-Mental State Examination score <24), neuropsychiatric, or medical conditions that could interfere with treatment or outcome assessment, and concurrent participation in another clinical trial. The complete eligibility criteria are provided in the published protocol [21].

The a priori sample size calculation assumed a between-group difference of 0.18 m/s in 10MWT change, a pooled SD of 0.20 m/s, a two-sided α of 0.05, 80% power, and 1:1 allocation. This required 21 evaluable participants per group; allowing for a 10% dropout rate yielded a target sample of at least 46 participants. A total of 48 participants were ultimately randomized.

B. Randomization and Masking

Participants were randomly assigned 1:1 to active iTBS or sham stimulation. A laboratory technician who was not involved in clinical treatment or outcome assessment generated the allocation sequence using computer-generated random numbers. Group assignments were concealed in sealed envelopes and released after completion of the baseline assessment. Investigators, physical therapists, participants, and outcome assessors were blinded to treatment allocation. Participants were instructed not to discuss their stimulation experience with outcome assessors or other participants during the trial.

C. Interventions

Both groups received individualized conventional rehabilitation throughout the 6-week study period. Conventional rehabilitation was delivered by experienced therapists for 40 min per

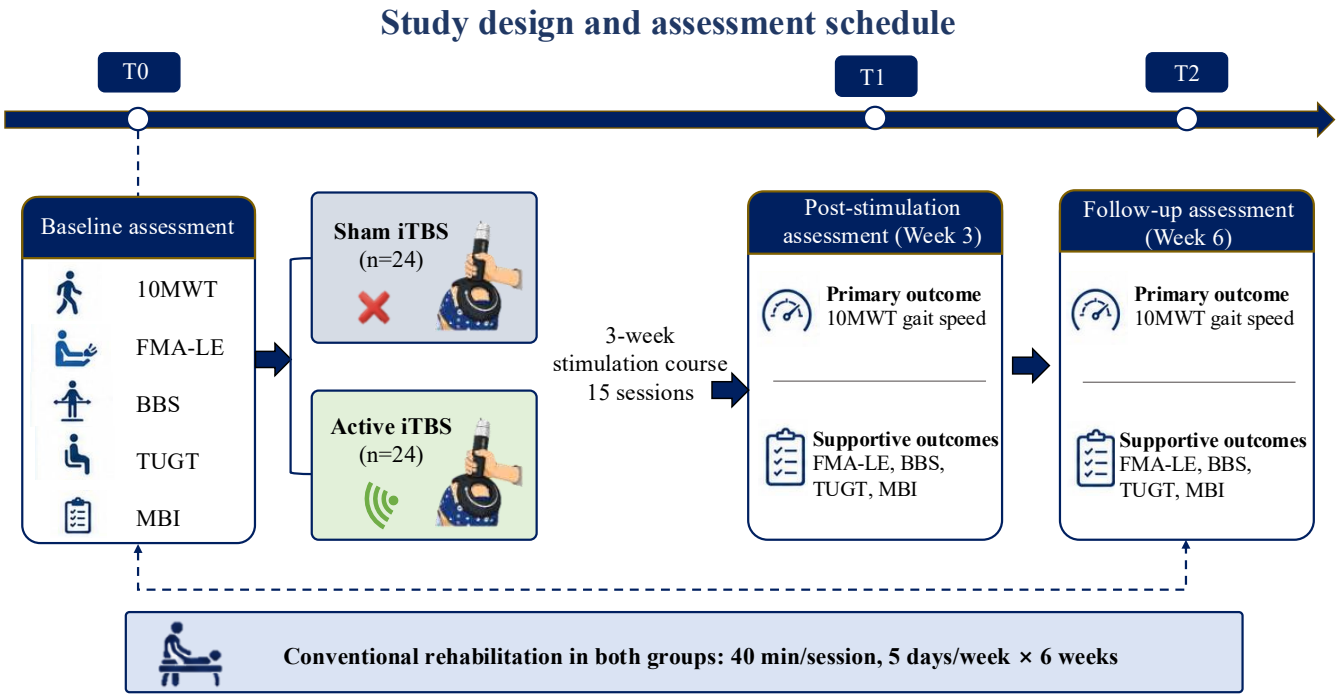

Fig. 1. Study design and assessment schedule. Participants received active or sham iTBS for 3 weeks (15 sessions) in addition to 6 weeks of conventional rehabilitation. Clinical assessments were performed at baseline, Week 3 immediately after the stimulation course, and Week 6 during continued rehabilitation.

session, five days per week. It included lower-limb motor training, strengthening, balance, gait, transfer, and functional mobility activities adapted to each participant's clinical status. Thus, conventional rehabilitation continued for 3 weeks after the iTBS or sham stimulation course ended at Week 3.

For cortical stimulation, the international 10–20 system was used for initial localization of the lower-limb motor area. The tibialis anterior motor hotspot was then identified using MEPs. Active motor threshold (aMT) was defined as the minimum stimulus intensity required to elicit a peak-to-peak tibialis anterior MEP >200 μV in at least 5 of 10 trials during active contraction. When a reliable hotspot could not be identified on the affected hemisphere, the hotspot was identified on the unaffected hemisphere and its homologous location was mirrored to the affected side for stimulation; in these cases, stimulation intensity was determined using the unaffected-side aMT.

Active iTBS was delivered using a Magneuro100 stimulator (Nanjing Vishee Medical Technology Co., Ltd., China) with a double-cone coil (VCZ001) positioned over the affected lower-limb motor representation. Each burst consisted of three pulses at 50 Hz, repeated at 5 Hz in 2-s trains every 10 s. Stimulation was delivered at 80% of individual aMT, with 600 pulses per session. Treatment was administered once daily, five days per week, for 3 weeks, resulting in a total of 15 sessions. Sham stimulation used a dedicated sham coil at the same target and followed the same temporal schedule, with similar acoustic clicks but without active iTBS (Fig. 1).

D. Outcomes and Assessment Schedule

Outcomes were assessed at baseline, immediately after the 3-week stimulation course (Week 3), and during continued conventional rehabilitation at Week 6. The protocol specified 10-Meter Walk Test (10MWT) performance as the primary outcome and included both post-baseline assessments. Week 3 was designated as the principal clinical contrast for the present analysis, whereas Week 6 assessed whether the between-group difference remained during continued rehabilitation.

The 10MWT was performed at the fastest safe walking speed along a 14-m walkway. The central 10 m was timed over three trials, converted to gait speed in meters per second, and averaged. Supportive outcomes included the Fugl–Meyer Assessment for the Lower Extremity (FMA-LE; 0–34 points), Berg Balance Scale (BBS; 0–56 points), Timed Up and Go Test (TUGT; seconds), and Modified Barthel Index (MBI; 0–100 points). High FMA-LE, BBS, and MBI scores and low TUGT values indicated better performance. The Functional Reach Test (FRT; cm) and posturography measures obtained using the Pro-Kin 254P platform (TecnoBody, Italy) were analyzed as exploratory outcomes.

For the secondary prediction analysis, Week 6 response was defined as an increase in 10MWT gait speed of $\geqslant$0.10 m/s from baseline. This threshold was selected as a clinically relevant benchmark based on previous stroke literature [22–24], rather than as a validated minimal clinically important difference specific to the fast 10MWT used in this study.

E. Safety Assessment

Adverse events were monitored throughout the study and reviewed against contemporaneous safety records. Recorded events included headache, scalp discomfort, fatigue, blood-pressure elevation, serious adverse events, and adverse-event-

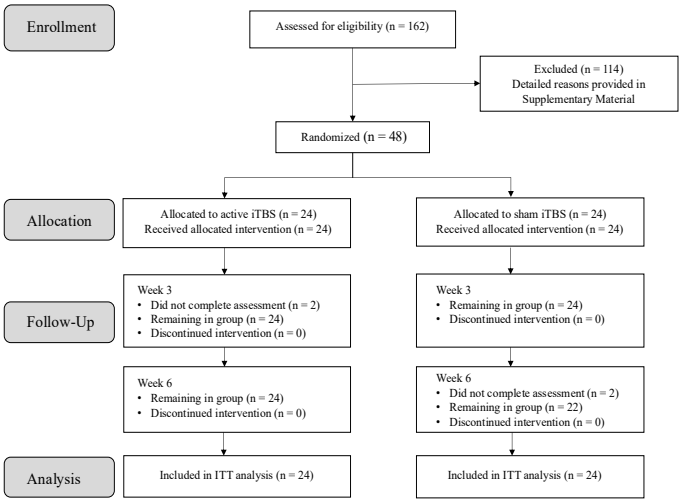

Fig. 2. CONSORT flow diagram of participant screening, randomization, follow-up, and analysis.

related treatment discontinuation or withdrawal. Event categories were summarized separately as n (%) because participants could experience more than one event. No serious adverse events or adverse-event-related treatment discontinuations or withdrawals were recorded.

F. Clinical Statistical Analysis

Clinical analyses followed the intention-to-treat principle, retaining all randomized participants in their assigned groups and using all available post-baseline observations without outcome imputation. For each outcome, a baseline-adjusted linear mixed-effects model included group, categorical time, group-by-time interaction, and the corresponding baseline value as fixed effects, with a participant-specific random intercept. Models were estimated using restricted maximum likelihood with two-sided Wald 95% confidence intervals. The active-versus-sham contrast at Week 3 was the principal clinical comparison, whereas Week 6 was the follow-up comparison during continued rehabilitation. Holm adjustment was applied across the eight post-baseline contrasts for FMA-LE, BBS, TUGT, and MBI, whereas exploratory FRT and posturography outcomes were controlled using the Benjamini–Hochberg false-discovery-rate procedure. A baseline-adjusted Week 3 ANCOVA was performed as a sensitivity analysis of the primary 10MWT result. Additional sensitivity and robustness analyses are described in Supplementary Methods S2 and Table S2.

G. Secondary Treatment-Informed Response Prediction

Prediction analysis included 46 participants with available baseline and Week 6 10MWT data. Response was defined as a ≥0.10 m/s increase in 10MWT gait speed from baseline to Week 6. The primary ridge logistic model combined baseline 10MWT, TUGT, FMA-LE, and randomized treatment assignment. A clinical only model and a treatment only benchmark were used to assess the complementary predictive contributions of baseline clinical status and treatment assignment.

Model performance was evaluated using repeated stratified fourfold cross-validation, with preprocessing and model tuning performed within the training data. Held-out predictions were summarized using AUROC, Brier score, and calibration measures, with uncertainty estimated by participant-level bootstrap. Sensitivity analyses examined the influence of baseline 10MWT and alternative formulations of the gait-speed outcome. Full model specifications, benchmark analyses, and additional sensitivity analyses are provided in the Supplementary Material. The prediction analysis was secondary to the randomized clinical analysis and was not designed to estimate individualized causal treatment effects.

TABLE I BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

Characteristic	Active iTBS (n=24)	Sham (n=24)
Age, y; mean ± SD	61.17 ± 9.11	61.38 ± 10.31
Sex, n (%)		
Male	18 (75.0)	17 (70.8)
Female	6 (25.0)	7 (29.2)
Weight, kg; mean ± SD	65.87 ± 10.13	67.44 ± 12.30
Height, cm; mean ± SD	166.58 ± 7.91	167.00 ± 8.56
Type of stroke, n (%)		
Ischemic	19 (79.2)	19 (79.2)
Hemorrhagic	5 (20.8)	5 (20.8)
Affected side, n (%)		
Left	12 (50.0)	13 (54.2)
Right	12 (50.0)	11 (45.8)
Time since stroke, mo; mean ± SD	4.96 ± 2.49	5.67 ± 2.46
Baseline 10MWT gait speed, m/s; mean ± SD	0.44 ± 0.24	0.40 ± 0.24
Baseline FMA-LE score; mean ± SD	18.71 ± 4.06	18.42 ± 4.77
Baseline TUGT, s; mean ± SD	39.55 ± 31.13	41.51 ± 22.31
Baseline MBI score; mean ± SD	73.04 ± 19.23	68.21 ± 13.34
Baseline BBS score; mean ± SD	31.42 ± 9.30	30.33 ± 10.90
Baseline FRT, cm; mean ± SD	16.18 ± 6.74	14.41 ± 5.44

Values are mean ± SD or n (%). Baseline characteristics are reported descriptively without significance testing. 10MWT, 10-m Walk Test; FMA-LE, Fugl-Meyer Assessment of the Lower Extremity; TUGT, Timed Up and Go Test; MBI, Modified Barthel Index; BBS, Berg Balance Scale; FRT, Functional Reach Test.

III. RESULTS

A. Participant Characteristics

Of 162 individuals assessed for eligibility, 48 participants were enrolled and randomly assigned to active iTBS (n=24) or sham stimulation (n=24) (Fig. 2). Baseline demographic and clinical characteristics are summarized in Table 1. At Week 3, 10MWT data were available for 22 participants in the active iTBS group and all 24 participants in the sham group; at Week 6, data were available for all 24 participants in the active group and 22 participants in the sham group. All 48 randomized participants were included in the intention-to-treat analysis using all available observations.

B. Clinical Outcomes

At Week 3, 10MWT gait speed favored active iTBS over sham stimulation (adjusted between-group difference, 0.112 m/s; 95% CI, 0.074–0.151; P<0.001). The between-group

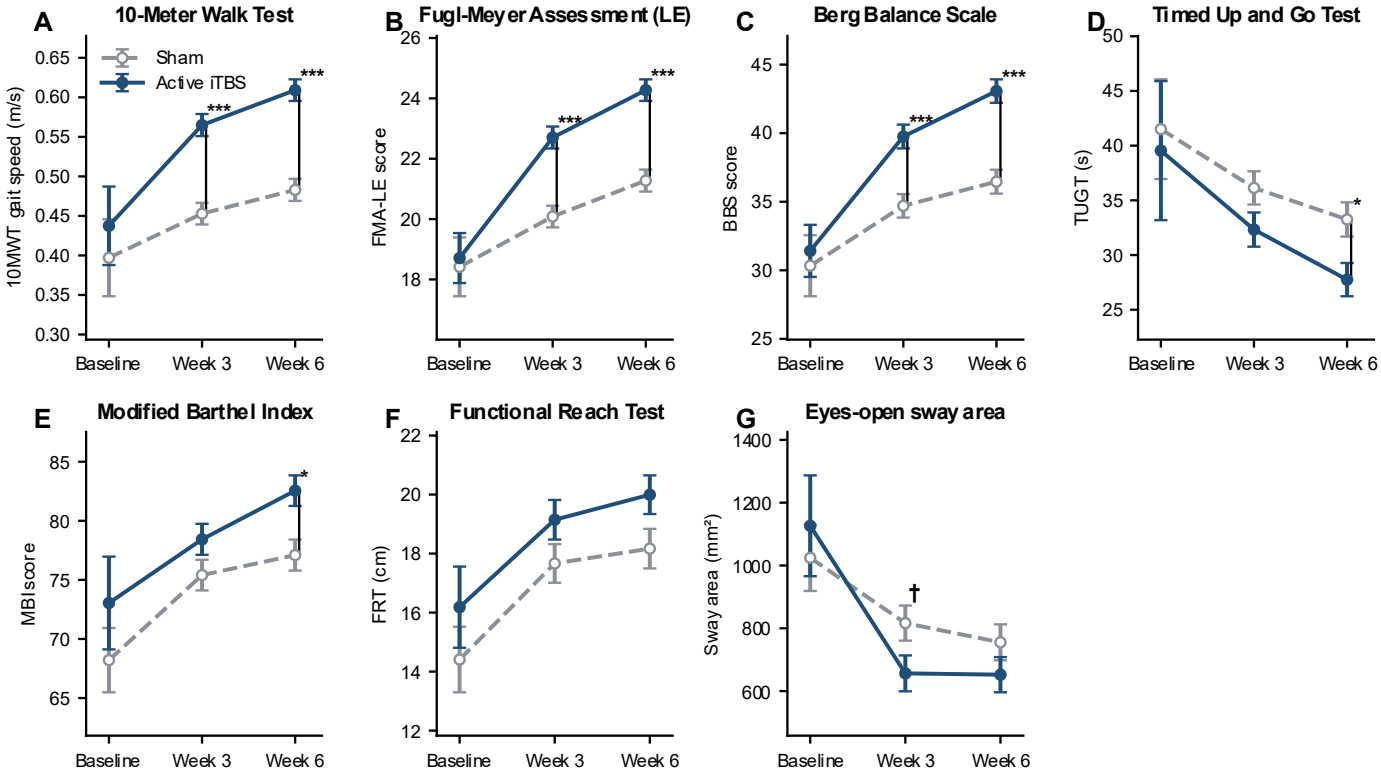

Fig. 3. Clinical outcomes from baseline to Week 6. Baseline values are unadjusted means ± SE; Week 3 and Week 6 values are baseline-adjusted estimated marginal means ± SE from random-intercept linear mixed-effects models. Group sizes were 24/24 at baseline, 22/24 at Week 3, and 24/22 at Week 6 for active iTBS/sham. Stars indicate between-group differences for 10MWT and Holm-adjusted differences for FMA-LE, BBS, TUGT, and MBI (*P<0.05, **P<0.01, ***P<0.001). † indicates a nominal exploratory difference at P<0.05 that did not survive Benjamini–Hochberg false discovery rate correction. Solid blue and dashed gray lines represent active iTBS and sham stimulation, respectively.

difference remained evident at Week 6 during continued rehabilitation (0.126 m/s; 95% CI, 0.088–0.165; P<0.001) (Table 2; Fig. 3).

Lower-limb motor impairment and balance showed consistent improvements. After Holm adjustment, FMA-LE favored active iTBS at Week 3 (adjusted difference, 2.62 points; 95% CI, 1.62–3.62; adjusted P<0.001) and Week 6 (3.00 points; 95% CI, 2.00–4.00; adjusted P<0.001). BBS similarly favored active iTBS at Week 3 (5.05 points; 95% CI, 2.66–7.45; adjusted P<0.001) and Week 6 (6.61 points; 95% CI, 4.21–9.00; adjusted P<0.001). TUGT showed no clear between-group difference at Week 3 (−3.81 s; 95% CI, −8.09 to 0.46; adjusted P=0.161) but favored active iTBS at Week 6 (−5.50 s; 95% CI, −9.78 to −1.23; adjusted P=0.035). MBI showed a similar pattern, with no clear difference at Week 3 (3.03 points; 95% CI, −0.60 to 6.66; adjusted P=0.161) and an increased score with active iTBS at Week 6 (5.45 points; 95% CI, 1.82–9.09; adjusted P=0.013).

Exploratory outcomes were inconsistent. FRT did not differ between groups at Week 3 (1.48 cm; 95% CI, −0.37 to 3.33; nominal P=0.116) or Week 6 (1.83 cm; 95% CI, −0.02 to 3.67; nominal P=0.052). Eyes-open sway area exhibited a significant decrease with active iTBS at Week 3 (−160.0 mm²; 95% CI, −316.9 to −3.1; nominal P=0.046), but this finding did not survive Benjamini–Hochberg false discovery rate correction (adjusted P=0.262) and was not maintained at Week 6 (−103.1 mm²; 95% CI, −260.1 to 53.9; nominal P=0.198). The baseline-adjusted Week 3 ANCOVA yielded a treatment estimate consistent with the primary mixed-effects analysis (Table S2).

C. Safety and tolerability

No serious adverse events, treatment discontinuations, or withdrawals due to adverse events were recorded. In the active iTBS group, headache occurred in 3 participants (12.5%), scalp discomfort occurred in 2 (8.3%), fatigue occurred in 13 (54.2%), and elevated blood pressure occurred in 3 (12.5%). In the sham group, fatigue occurred in 15 participants (62.5%) and elevated blood pressure occurred in 4 (16.7%); no headache or scalp discomfort was recorded. Overall, recorded adverse events were mild or comparable between groups.

D. Week 6 response

Among the 46 participants with available baseline and Week 6 10MWT data, 23 met the predefined response threshold of a ≥0.10 m/s increase in gait speed. Response occurred in 19 of 24 participants receiving active iTBS (79.2%) and 4 of 22 receiving sham stimulation (18.2%). Two sham participants without Week 6 10MWT data were excluded from the prediction analysis.

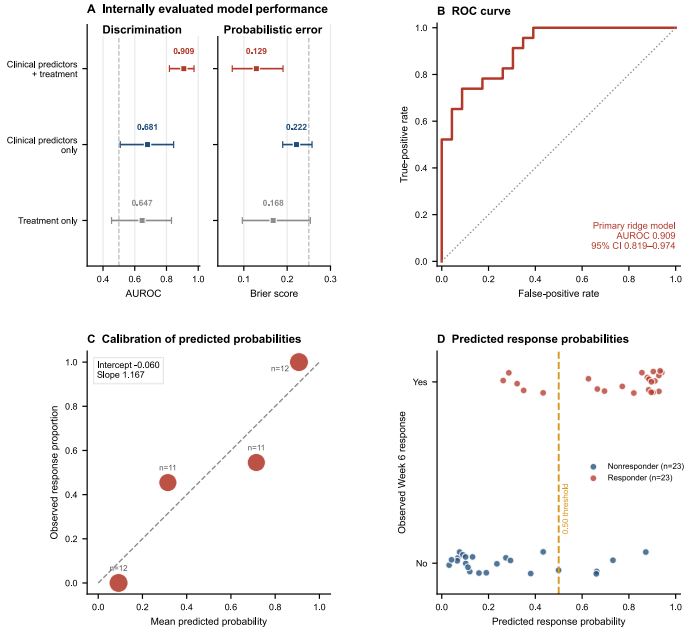

Fig. 4. Internal evaluation of treatment-informed Week 6 response prediction. (A) Performance of the treatment only benchmark, clinical only model (baseline 10MWT, TUGT, and FMA-LE), and primary treatment-informed ridge model. Adding randomized treatment assignment to the clinical predictors increased AUROC by 0.229 and reduced the Brier score by 0.093. AUROC and Brier score were calculated from aggregated out-of-fold predictions; lower Brier scores indicate better probabilistic accuracy, and error bars represent bootstrap 95% CIs. (B) Receiver operating characteristic curve for the primary model. (C) Calibration of predicted versus observed response; the diagonal indicates perfect calibration. (D) Predicted response probabilities according to observed response status; the dashed line indicates the 0.50 classification threshold. Response was defined as a ≥0.10 m/s increase in 10MWT gait speed from baseline to Week 6. FMA-LE, Fugl–Meyer Assessment of the Lower Extremity; TUGT, Timed Up and Go Test; 10MWT, 10-Meter Walk Test.

E. Prediction performance

The primary treatment-informed ridge model achieved an internally evaluated AUROC of 0.909 (bootstrap 95% CI, 0.819–0.974) and a Brier score of 0.129, with a calibration intercept of −0.060 and slope of 1.167. Compared with the clinical only model, adding received treatment increased AUROC by 0.229 and reduced the Brier score by 0.093. The treatment only benchmark yielded an AUROC of 0.647 and a Brier score of 0.168. Excluding baseline 10MWT produced similar discrimination, although the Brier score increased. Full benchmark, calibration, and sensitivity results are reported in the Supplementary Material.

IV. Discussion

This randomized sham-controlled trial showed that double-cone-coil iTBS added to conventional rehabilitation improved gait speed after stroke. The principal comparison in Week 3 demonstrated an adjusted between-group difference of 0.11 m/s in 10MWT gait speed, accompanied by consistent improvements in lower-limb motor impairment and balance as measured by FMA-LE and BBS. The gait speed advantage remained evident at Week 6 as both groups continued conventional rehabilitation. TUGT and MBI showed later between-group differences at Week 6, whereas exploratory FRT and posturography findings were inconsistent. As a secondary extension, treatment-informed clinical modeling showed promising internal discrimination of Week 6 response. Overall, the findings support the clinical benefit of the double-cone-coil iTBS protocol and suggest that baseline clinical status together with treatment assignment may help characterize variability in recovery.

The observed gait-speed benefit is clinically relevant. Walking speed is closely related to functional ambulation after stroke, and transitions across speed-based categories have been associated with improvements in mobility and participation [3, 4, 34]. The adjusted between-group difference of 0.11 m/s at Week 3 falls within the range reported as meaningful for gait-speed improvement [22], although estimates vary according to stroke phase, walking condition, and the method used to define meaningful change [23, 24]. Thus, the magnitude of the present effect supports a clinically relevant improvement in walking performance rather than merely a statistical separation between groups. However, clinic-based gait speed captures only one dimension of mobility. Community ambulation also depends on balance, endurance, motor impairment, environmental demands, and assistive-device use [35, 36]. Direct monitoring of daily walking activity will therefore be needed to determine whether the observed gains translate into greater mobility and participation in everyday life.

The favorable clinical outcomes strengthen the interpretation of the primary gait result. FMA-LE and BBS favored active iTBS at both post-baseline assessments after multiplicity adjustment, indicating that the treatment effect was not confined to walking speed alone. TUGT and MBI showed no clear between-group differences immediately after the stimulation course but favored active iTBS at Week 6, suggesting that improvements in overall mobility and independence may emerge later than changes in gait speed or motor impairment. These later findings should be interpreted with caution because they represent supportive rather than primary outcomes. Exploratory posturography showed a nominal reduction in eyes-open sway area at Week 3, which was directionally consistent with improved balance but did not survive false-discovery-rate correction and was not maintained at Week 6. This finding should therefore be regarded as hypothesis-generating rather than confirmatory evidence of improved postural control.

The interpretation of Week 6 requires particular temporal caution. The iTBS or sham stimulation course ended at Week 3, whereas conventional rehabilitation continued in both groups through Week 6. Thus, the Week 6 comparison indicates that the randomized between-group advantage remained evident during ongoing rehabilitation; it should not be interpreted as a definitive

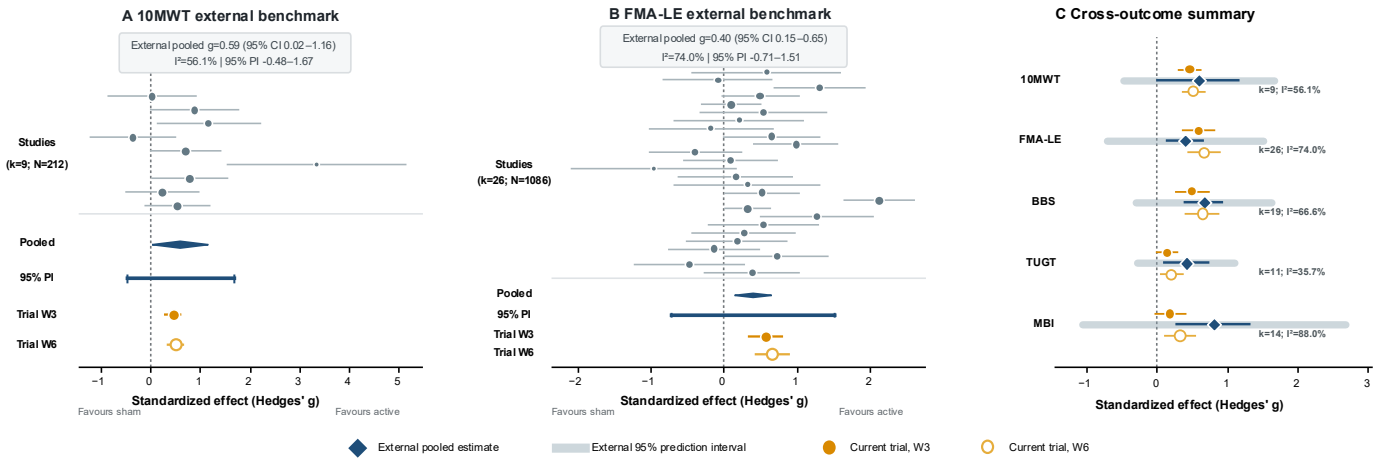

Fig. 5. External literature benchmark for lower-limb outcomes. Panels A and B show external study estimates, pooled effects, 95% prediction intervals, and the present trial's Week 3 and Week 6 estimates for 10MWT and FMA-LE. Panel C summarizes all five outcomes. Positive values promote active stimulation; the present trial contributed zero weight to the external pooling.

estimate of durability after all protocolized treatment had ended. The continued between-group difference could reflect a residual effect of prior stimulation, an interaction between prior stimulation and ongoing rehabilitation, or both. The present design cannot distinguish among these possibilities. Longer follow-up after completion of all protocolized treatment, ideally with prospective monitoring of participant-level rehabilitation exposure and real-world activity, will be needed to determine the durability of the treatment effect.

The present intervention was motivated by the practical difficulty of stimulating the lower-limb motor representation. The leg motor area lies deep and medially near the interhemispheric fissure, tibialis anterior hotspots vary substantially between individuals and after stroke, and lower-limb stimulation recruits corticospinal output differently from more superficial motor representations [7, 8]. Double-cone coils improve access to deeper lower-limb representations relative to conventional coils, although greater depth is accompanied by reduced focality [9, 10]. iTBS offers an additional practical advantage because a complete stimulation session can be delivered within a relatively short rehabilitation workflow [11]. Previous double-cone and lower-limb stimulation studies established feasibility and suggested potential functional benefits [12–14, 38–40], and recent meta-analyses indicate possible improvements in lower-limb motor and balance outcomes [15, 41]. Simultaneously, the literature exhibits variability in coil design, stimulation target, intensity, laterality, stroke phase, concurrent rehabilitation, and assessment timing. Therefore, the current trial supports the efficacy of the specific intervention tested here rather than a generalized conclusion for all lower-limb rTMS or iTBS protocols.

To place the randomized effects in a broad context, we compared the present estimates with previously assembled randomized studies of lower-limb stimulation (Fig. 5). External pooled standardized effects were moderate for 10MWT and FMA-LE, but the wide 95% prediction intervals crossed zero, reflecting substantial between-study heterogeneity. The present Week 3 and Week 6 estimates fell within these broad external distributions and were not included in the pooled estimates. Similar heterogeneity was evident across BBS, TUGT, and MBI. Thus, this benchmark places the present findings within the range of prior evidence rather than providing external validation. Differences in stimulation protocol, outcome definition, timing, and patient characteristics preclude direct claims of superiority, equivalence, or noninferiority between stimulation approaches.

Considerable heterogeneity in recovery remained despite the average treatment benefit observed in the randomized comparison. Previous longitudinal studies have shown that baseline walking performance contains prognostic information but does not determine an individual's later trajectory [5, 6]. Lower-extremity MEPs and trial-based biomarker studies have similarly demonstrated that clinical and neurophysiological characteristics provide complementary information about later lower-limb recovery [16, 17]. Neuroimaging and electrophysiological studies further indicate that gait impairment after stroke reflects distributed abnormalities extending beyond a single behavioral measure [42, 43]. In parallel, physiological responses to theta-burst stimulation show marked interindividual variability [44, 45], and attempts to predict such variability remain preliminary [46]. These observations provide a rationale for examining heterogeneity in clinical responses, but they should not be interpreted as a demonstrated mechanism for the present treatment effect because no mechanistic neurophysiological mediator was evaluated in this analysis.

The secondary predictive analysis was deliberately parsimonious. Baseline 10MWT, TUGT, and FMA-LE represent complementary aspects of walking capacity, integrated mobility, and lower-limb motor impairment, whereas randomized treatment assignment provides information about the intervention received. Combining these variables produced substantially better discrimination and probabilistic accuracy than the clinical-only model, suggesting that baseline clinical status and treatment assignment contributed complementary predictive information. This finding is clinically interesting because it indicates that the observed response was not explained solely by baseline clinical status or by treatment assignment. However, the model predicts the probability of the observed Week 6 response based on baseline status and the treatment

received. It does not estimate the outcome that the same individual would have experienced under the alternative treatment, so it cannot be interpreted as an individualized causal treatment selection model [47, 48].

The internal prediction results should also be interpreted considering the small sample size. Repeated held-out evaluation reduced training-set optimism by assessing discrimination, Brier score, and calibration using predictions generated outside the corresponding training folds [26–29]. Nevertheless, only 46 participants with 23 responders were available for prediction, and internal resampling cannot replace independent validation [27, 31, 33]. The AUROC of approximately 0.91 should therefore be regarded as proof-of-concept evidence rather than evidence of a clinically applicable model. Calibration was encouraging at the point-estimate level but remained imprecisely estimated in a cohort of this size. Similar performance across alternative algorithms further suggests that the predictive signal arose primarily from the information contained in the selected variables rather than from a particular machine learning method. Because baseline 10MWT was included as a predictor and also contributed to the change-based response definition, mathematical coupling and regression to the mean were additional concerns. Removing baseline 10MWT yielded similar discrimination but a higher Brier score, suggesting that mathematical coupling alone did not account for the observed discrimination, while recognizing that the change-based response definition remained inherently dependent on baseline gait speed.

The prediction component therefore extends rather than replaces the randomized clinical finding. Previous rehabilitation engineering studies have used neurophysiological or multimodal behavioral information to predict lower-limb motor gains and treatment response [18, 19], while PREP2 provides a broader example of structured stroke recovery prediction [20]. The present study differs by using a deliberately simple clinical model within a randomized efficacy trial and examining baseline clinical status with randomized treatment information in the same participants. This design provides a practical bridge between average treatment efficacy and variability in observed responses using information readily available in routine clinical practice. Future multicenter work should prospectively apply the frozen model and response definition to independent cohorts; assess calibration and clinical utility across centers and devices; and determine whether lesion characteristics, TMS measures, EEG, or imaging features add reproducible predictive value beyond the clinical baseline.

Several limitations should be considered. First, this work was a relatively small, single-center randomized trial, which limits precision and generalizability, particularly for the secondary predictive analysis. Second, Week 6 occurred during ongoing conventional rehabilitation rather than after completion of all treatment, preventing a definitive assessment of post-treatment durability. Third, participant-level rehabilitation exposure was unavailable in sufficient detail to quantify actual treatment dose across individuals, although both randomized groups followed the same protocolized rehabilitation schedule. Fourth, predictive analysis was based on 46 participants and a change-based response definition that included baseline 10MWT in the target and the primary predictor set; sensitivity analysis reduces but does not remove this concern. Fifth, the prediction model underwent only internal evaluation and did not estimate individualized causal treatment effects or support treatment selection. These limitations particularly constrain interpretation of the predictive findings, while the randomized treatment contrast remains the principal efficacy result.

V. Conclusion

Double-cone-coil iTBS added to conventional rehabilitation improved gait speed after stroke, yielding concordant benefits in lower-limb motor impairment and balance. The randomized gait speed advantage remained evident at Week 6 during continued rehabilitation. Treatment-informed clinical prediction provided a complementary proof-of-concept approach for characterizing heterogeneity in observed responses, warranting evaluation in larger independent cohorts.

Availability of data and materials

Deidentified data and analysis code are available from the corresponding authors upon reasonable request, subject to ethics and institutional approval.

Disclosures

All authors declare no conflicts of interest.

Authors' Contributions

Hewei Wang and Jianxia Lu conceptualized and designed the study. Yao Qian and Bin Su conducted the study and collected data. Yue Sun, Hongrui Liu and Limin Sun directly accessed and verified the underlying original data. Zhipeng Pan and Yi Shao conducted the formal statistical analysis. Bin Su and Yue Sun drafted the manuscript. Illustrations were created by Tianyu Ma and Shan Lu. All authors critically revised the manuscript. Hewei Wang and Jianxia Lu supervised the study. All authors approved the final manuscript.

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