Clinical Neurophysiology 178 (2025) 2110957

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

High-frequency rTMS and home-based exercise in individuals with Parkinson's disease: A double-blind randomized controlled trial

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ARTICLE INFO

Keywords:
Parkinson's disease
Repetitive transcranial magnetic stimulation
Home-based exercise
Locomotion
Randomized controlled trial

ABSTRACT

Objective: This study aimed to investigate the effects of combining repetitive Transcranial Magnetic Stimulation (rTMS) with home-based exercise (HB) over 10 sessions and examined locomotion outcomes over 8 weeks in individuals with Parkinson's disease (PD).
Methods: Thirty-nine individuals with mild to moderate PD were randomly assigned to real rTMS combined with HB (real rTMS + HB), sham rTMS combined with HB (sham rTMS + HB), and a control group. The intervention groups received 10 sessions of rTMS alongside an 8-week HB program.
Results: Significant improvements ($p < 0.05$) were found in both intervention groups over time for clinical outcomes and turning characteristics compared to the control group. No significant clinical or kinematic differences were observed between the real and sham rTMS + HB groups. Only the real rTMS + HB group showed reduced motor-evoked potential amplitude after 10 sessions and at 8-week follow-up.
Conclusion: Home-based exercise improved locomotion in individuals with PD. Although real rTMS modified cortical excitability, it did not provide additional clinical or kinematic benefits beyond home-based exercise alone.
Significance: The combination of rTMS combined with home-based exercise may influence cortical excitability; however, locomotion improvements in individuals with PD appear to be primarily driven by home-based exercise, and the neuromodulatory role of rTMS warrants further investigation.

1. Introduction

Parkinson's disease (PD) is a progressive movement disorder caused by dopaminergic neuron loss in the substantia nigra pars compacta, leading to α-synuclein aggregation and dysfunction of the basal ganglia (Bloem et al., 2021, Rousseaux et al., 2017). Most individuals with PD experience significant difficulties with locomotion, including gait and turning problems, which increase the risk of falling (Morris, 2006, Smith et al., 2021).

Combining medication with exercise therapy has shown promise in improving functional movement in individuals with PD and is recommended in clinical practice guidelines (Osborne et al., 2021). Numerous studies have demonstrated the benefits of physiotherapy and exercise in managing turning difficulties in PD (Choi et al., 2020, Flynn et al., 2019, Khobkhun et al., 2021a, Khobkhun et al., 2021b, Pohl et al., 2020, Radder et al., 2020, Rawson et al., 2019, Wroblewska et al., 2019).

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https://doi.org/10.1016/j.clinph.2025.2110957
Accepted 25 July 2025
Available online 30 July 2025

Additionally, there is evidence supporting the efficacy of both supervised physiotherapist-led rehabilitation (Dereli and Yaliman, 2010, Khalil et al., 2017) and unsupervised home-based exercise programs (Khobkhun et al., 2021a, Khobkhun et al., 2021b, Pohl et al., 2020). Home-based exercises, often considered a "bottom-up" approach, have shown positive effects on gait, turning kinematics, and self-reported outcomes in individuals with PD (Khobkhun et al., 2021a, Khobkhun et al., 2021b). This approach typically requires a treatment period of 6 to 10 weeks, similar to programs used in stroke rehabilitation (Thanakamchokchai et al., 2015, Tretriluxana et al., 2018).

Recently, technology has played an increasingly significant role in neurorehabilitation, particularly in modulating neurophysiological activation through a "top-down" approach (Niemrungruang et al., 2024). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has emerged as an alternative treatment for various neurological and psychiatric conditions, including stroke, PD, and depression (Janicak and Dokucu, 2014, Nardone et al., 2020, Thanakamchokchai et al., 2020a, Tung et al., 2019). Recent studies suggest that high-frequency rTMS (HF-rTMS) over the supplementary motor area (SMA) may serve as an effective adjunct therapy for alleviating gait freezing and enhancing turning function in individuals with PD (Kim et al., 2018, Li et al., 2022, Ma et al., 2019, Mi et al., 2019). Interestingly, Kim and colleagues (2018) indicated that the SMA is a more appropriate site for stimulation to alleviate freezing of gait (FOG) compared to the primary motor cortex (M1) (Kim et al., 2018). Their study found that two sessions of HF-rTMS over the SMA significantly improved FOG, reducing the number of steps, shortening walk time, and decreasing the frequency of freezing episodes during the stand-walk-sit (SWS) test. Similarly, Mi et al. in 2019 (Mi et al., 2019) reported improvements in the Movement Disorder Society- the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores, FOG questionnaire scores, and various gait variables, including stride length, stride velocity, double support time percentage, and sit-to-stand duration, following HF-rTMS over the SMA. These effects, due to the cumulative impact of HF-rTMS over at least 5 consecutive sessions, persisted for up to 6 weeks after 10 sessions of stimulation.

The pathophysiology of PD suggests that locomotion issues, including FOG and turning deficits, may result from dysfunctions in the supraspinal locomotor networks, including the M1, SMA, parietal cortex, basal ganglia, subthalamic nucleus, mesencephalic locomotor region, and cerebellum (Pozzi et al., 2019). In particular, a decrease in SMA activity in individuals with PD has been linked to FOG, potentially due to reduced positive efferent feedback from the basal ganglia-thalamocortical pathway (Gao et al., 2017, Haslinger et al., 2001, Herz et al., 2014, Jenkins et al., 1992, Lu et al., 2024, Shine et al., 2013, Snijders et al., 2021, Wu and Hallett, 2005). Since the SMA plays a crucial role in self-initiated movements, movement preparation, sequencing, and performance of complex tasks, including gait (Haslinger et al., 2001, Niemrungruang et al., 2024, Tessitore et al., 2019, Wu and Hallett, 2005), HF-rTMS may be beneficial in alleviating FOG in individuals with PD.

Interestingly, improvements in FOG have been observed after just two sessions of HF-rTMS, reducing the treatment duration compared to other rehabilitation methods such as home-based exercise programs. However, achieving long-term effects with rTMS requires cumulative sessions, with at least 10 sessions being reported in the literature, which increases treatment costs. To enhance long-term effects and reduce costs, a combined approach has been suggested (Niemrungruang et al., 2024, Tretriluxana et al., 2018, Yang et al., 2013). Home-based exercise programs may support the effects of HF-rTMS, with the combined effects potentially lasting for more than 6 weeks. Consequently, the aim of this study was to investigate the effects of 10 sessions of HF-rTMS over the SMA in combination with a home-based exercise program and to examine the effect at 8 weeks on gait and turning dysfunction in individuals with PD. Our hypothesis was that 10 sessions of HF-rTMS over the SMA combined with a home-based exercise program would significantly improve gait and turning performance, with these improvements being sustained over 8 weeks in individuals with PD.

2. Methods

2.1. Study design

This study was a randomized, double-blind, sham-controlled trial. Participants included individuals who were diagnosed with idiopathic PD based on the 2015 clinical diagnostic criteria for PD (Postuma et al., 2015). They were recruited from the Movement Disorder Clinic, Division of Neurology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand and diagnosed by neurologists (PS, YP and WS).

2.2. Participants

Sample size was calculated using G*Power version 3.1.9.7, applying the MDS-motor score from a previous study employing a similar rTMS methodology (Mi et al., 2019), based on a priori tests for a Mixed Model analysis of variance with three groups and three times point assessment. The level of significance (alpha) was set at 0.05, with a statistical power of 0.9, and the critical F value at 2.48. Based on these parameters, the estimated sample size was 15 participants per group, a total of 45 participants across the three groups.

Participants were randomly assigned to one of three parallel groups: a real HF-rTMS and home-based group (real rTMS + HB), a sham HF-rTMS and home-based group (sham rTMS + HB), and a control group that received only medication as a traditional treatment. Randomization was conducted using a computer-generated random number sequence by an individual not involved in the study. Allocation information for each participant was sealed in envelopes and placed in their respective folders to maintain confidentiality. Inclusion criteria were as follows: 1) a clinical diagnosis of PD at stages 2 to 3 assessed using the modified Hoehn and Yahr scale; 2) age between 50 and 75 years; 3) regular PD medication usage for at least a month; 4) ability to use a smartphone for downloading a metronome application; 5) ability to walk independently without any assistive device; and 6) capability to follow commands and instructions. Exclusion criteria included: 1) a clinical diagnosis of dementia; 2) cognitive impairment assessed by the Thai Mental State Examination < 24 (Tanglakmankhong et al., 2022) and the Montreal Cognitive Assessment (MoCA) with cut-off points stratified by education level: $\leq$14/23 for no education; $\leq$17/30 for elementary education; and $\leq$ 22/30 for higher education (Julayanont et al., 2015); 3) other neurological conditions that could affect test performance and gait function e.g. Idiopathic Normal Pressure Hydrocephalus, stroke induced PD, choreoathetosis and epilepsy; 4) high blood pressure (more than 140/90 mmHg at rest, measured three times with a 10-minute rest between each measurement) (Bushman, 2016); 5) undergoing haemodialysis; 6) uncorrectable visual problems; 7) positive screening for contraindications to TMS, confirmed via a TMS screening questionnaire; 8) implanted deep brain stimulation or plans for deep brain stimulation surgery during the study; 9) poorly controlled depression or anxiety, as measured by the Thai Hospital Anxiety and Depression Scale (score $\geq$ 11); and 10) ON/OFF medication fluctuations that could interfere with task performance or confound kinematic data interpretation. Participants with severe dyskinesia or motor fluctuations (MDS-UPDRS score $\geq$ 3) were also excluded. Clinical fluctuations were assessed using the MDS-UPDRS to determine the presence of ON/OFF medication fluctuations. All participants provided informed consent, approved by the Ethical Committee of Mahidol University Institutional Review Board, Mahidol University, Thailand (COA No. MU-MOU 2022/135.2012). All procedures adhered to the Declaration of Helsinki, and the study was registered with the Thai Clinical Trials Registry (TCTR) number TCTR20230127001.

2.3. Experimental procedures

Data collection was conducted at the Parkinson Movement and Research Collaboration Laboratory (PMARC lab), Faculty of Physical Therapy, Mahidol University. All measurements and treatments were conducted during the 'ON' state, with participants taking their medication 30–45 minutes (min) before each measurement and treatment session. Demographic data, clinical outcome measures, turning kinematics and stepping characteristics and cortical outcomes were measured for all participants at three time points: 1) baseline (T0), 2) after 10 sessions of the intervention (T1), and 3) post-intervention at week 8, within 2 days after completing the home-based training (T2) (Fig. 1).

All assessors were blinded to the group allocation and included a clinical physiotherapist (PR) for clinical and turning kinematic outcomes, and TMS specialists (JT and ST) for cortical outcomes. Based on previous research (Mi et al., 2019), 10 sessions of rTMS have been shown to sustain gait performance for 4 to 8 weeks. Since our study combined rTMS with a home-based exercise program, we anticipated that the intervention effects would persist longer than those with rTMS alone, which is why the final assessment was conducted at the 8th week. The flow of participants is detailed in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Fig. 2).

2.4. Primary and secondary outcomes

2.4.1. Primary outcomes

2.4.1.1. Clinical outcome measures

2.4.1.1.1. The Movement Disorder Society sponsored revision of the Unified Parkinson's disease Rating Scale (MDS-UPDRS). is an easy to use instrument typically requiring 15 to 20 min for administration (Goetz et al., 2008). The total motor scores range from 0 to 132, with higher scores indicating more severe disability. MDS-UPDRS Part III (motor scores) were reported separately from the total score to provide a more comprehensive evaluation of the effect of the intervention on motor function in individuals with PD.

2.4.1.1.2. The time up and Go test (TUG). was used to assess balance and mobility. Participants completed three attempts of rising from a chair, walking 3 m, returning to the chair, and sitting down again. The time was recorded, with faster times indicating better balance and mobility.

2.4.1.1.3. The 10-Meter walk test (10-MWT). was used to measure gait speed. Participants walked at a comfortable pace for both normal and fast speeds. The time taken to cross the 10-meter distance was recorded, and gait speed was calculated by dividing the distance by the time taken. The average time was reported for each participant, with faster times indicating better gait performance.

2.4.1.1.4. The freezing of gait questionnaire (FOG-Q). is a 6-question, clinician-administered, patient-reported rating scale designed to assess the severity and frequency of freezing of gait (FOG) and has been recommended in the evaluation of FOG in individuals with PD (Giladi et al., 2009).

2.4.1.2. Turning kinematics and stepping characteristics. Turning kinematics and stepping characteristics were recorded as participants performed a 180° turn on level ground from a standing position using Inertial Measurement Units (IMU) (XSENS, Ltd.). IMUs were attached to body segments, including the center of the head, middle thorax, pelvis, and center of the left and right feet (Khobkhun et al., 2022b, Khobkhun et al., 2021a). All participants were asked to stand approximately 1-meter in front of a projector screen and perform a 180° turn at their self-selected speed. Two trials were recorded in both the left and right directions using a visual cue controlled by a LabVIEW program (Fig. 3). A dual low-pass fourth-order Butterworth filter with a 6 Hz cut-off frequency was applied to the IMU data before calculating turning kinematics. Parameters reported included: 1) percentage onset time (in seconds) (Measured for the head, thorax, pelvis, and feet, with a lower percentage indicating earlier initiation), 2) peak head yaw velocity (in degrees/second), and 3) peak head-segment angular separation angle (in degrees). Displacement profiles were differentiated to produce velocity and acceleration profiles for each segment. Rotation onset for each segment was defined as the earliest time point before a segment displacement of 5 degrees with a velocity greater than 0 degrees/second. The rotation end was defined as the first zero crossing in the velocity profile after segment rotation completion. Stepping characteristics recorded included step count (number) and step size (degrees). Temporal characteristics of individual steps, such as step onset time and step duration (seconds), were calculated using step onset and placement times during the turn. The yaw rotation (degrees) of each foot during the swing phase of each step was used to calculate the average step size. Data processing was conducted using a validated program for assessing axial segment coordination during turning, following previously published research (Khobkhun et al., 2022b, Khobkhun et al., 2021a).

2.4.1.3. Cortical outcomes measurement: Corticospinal excitability and cortical inhibition variables. Cortical outcomes, including corticospinal excitability and cortical inhibition variables, were measured using Transcranial Magnetic Stimulation (TMS). Corticospinal excitability was assessed by measuring the resting motor threshold (rMT), motor-evoked potential (MEP) amplitude, and input–output curve, all of which were evaluated using single-pulse TMS with a double cone coil that is a monophasic TMS (Magstim 200^2, Magstim Co., Dyfed, UK). The coil was positioned tangentially over the left primary motor cortex (M1) at the optimal site for monitoring of the tibialis anterior (TA) muscle, defined as "the location where stimulation at a slightly suprathreshold intensity elicited the largest MEP in the target muscle". Electromyographic (EMG) (Medelec Synergy, VIASYS Health Care Inc., Surrey, UK) recordings were taken from the skin overlying the TA muscle to capture the MEPs. According to the corticospinal excitability assessment order, the resting

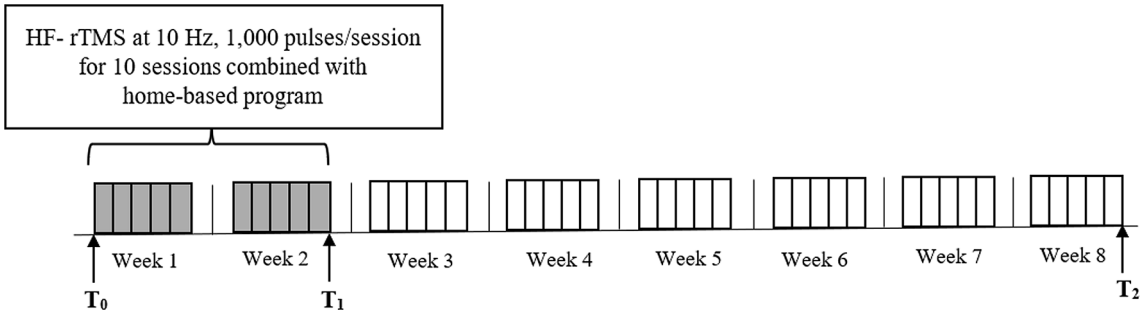

Fig. 1. Flow chart of the experimental design.

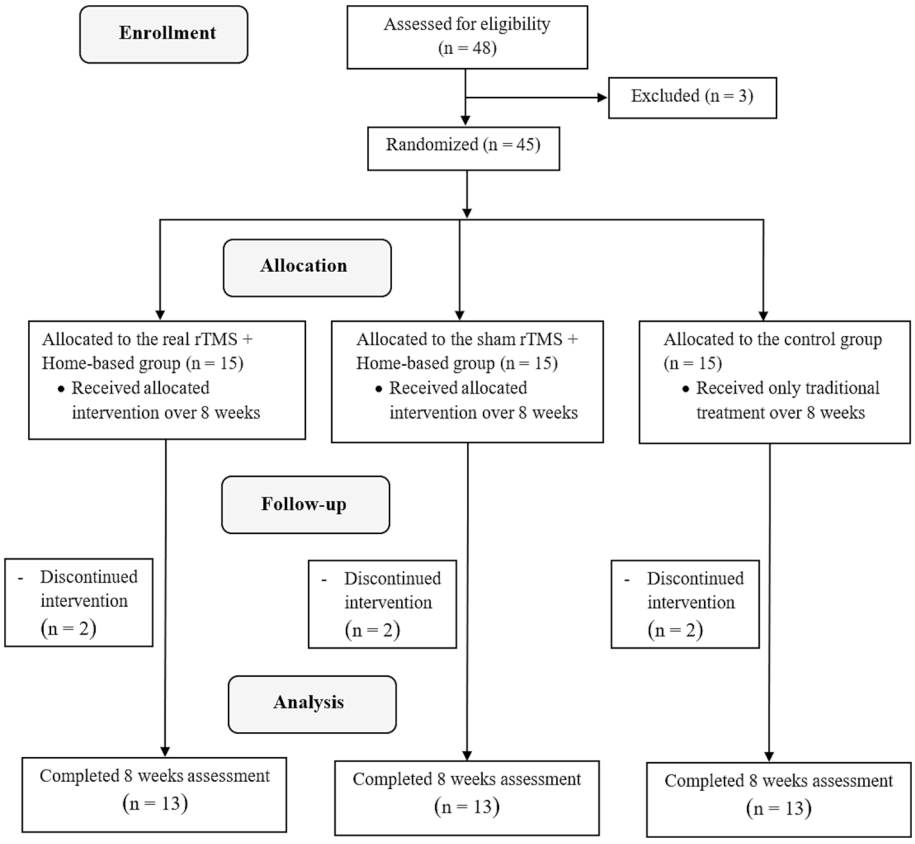

Fig. 2. CONSORT flow diagram.

motor threshold (rMT) was determined first. The rMT is defined as the minimum stimulus intensity required to produce a peak-to-peak amplitude of 50 μV or more in the target muscle in at least 5 out of 10 trials. After establishing the rMT, the motor-evoked potential (MEP) amplitude was recorded 10 times at stimulation intensities ranging from 110 % to 140 % of the rMT. The MEP amplitude recorded at 120 % of the rMT was specifically highlighted as a cortical excitability variable, while all data points were used to plot and report the slope input–output curve (Thanakamchokchai J, 2020a, Thanakamchokchai et al., 2020b). For the slope of the input–output (I/O) curve, measurements were taken at four stimulation intensities, increasing in 10 % increments from 110 % to 140 % of the rMT. The slope of the I/O curve, which reflects the gain in MEP amplitude with increasing stimulus intensity, was recorded 10 times at each intensity (Fadini et al., 2009).

Cortical inhibition was assessed using the cortical silent period (CSP), representing the duration of the interruption of voluntary motor activity following TMS (CSP duration). The CSP includes the relative CSP which is measured from the onset of MEP amplitude to the onset of re-emergence of background EMG activity. In contrast, the absolute CSP can be measured from the end of MEP to the onset of re-emergence of background EMG activity. The CSP was measured using single-pulse TMS with a double cone coil positioned at the same site used for measuring MEP amplitude. Participants were instructed to contract the TA at 10 % of their maximal voluntary contraction. Once participants maintained this contraction for 2 seconds, TMS was delivered at 120 % of the rMT. The CSP was evaluated over five trials (Thanakamchokchai J, 2020a, Thanakamchokchai et al., 2020b).

2.4.2. Secondary outcomes

The secondary outcomes included clinical measures related to gait and turning performance.

2.4.2.1. The functional Reach test (FRT). is a clinical assessment of balance control. A yardstick was positioned on the wall at the height of the acromion. Participants were asked to stand with their dominant arm at 90 degrees of shoulder flexion. They were then instructed to reach forward as far as possible along the yardstick scale, measured in inches, without taking a step, while the researcher recorded the value (Schenkman et al., 1998). Participants performed the test three times, and the average of these trials was recorded. A greater distance indicated better balance control.

2.4.2.2. The fall Efficacy Scale – International (FES-I). is a self-reported questionnaire assessing fear of falling. Participants rated their concerns about the possibility of falling while performing 16 activities on a four-point Likert scale (1: not at all concerned to 4: very concerned), with higher scores indicating a greater fear of falling (Thiamwong, 2011, Yardley et al., 2005).

2.4.2.3. Global Rating of change (GRoC). is a self-assessment tool measuring perceived change using an 11-point Likert scale. A GROC score of zero indicates no change, while scores ranging from + 1 to + 5 indicate increasing levels of perceived improvement, and scores from −1 to −5 indicate perceived deterioration. A threshold of ± 2 is considered clinically significant (Kamper et al., 2009).

2.5. Application of High-Frequency rTMS (HF-rTMS) at a treatment session

The HF-rTMS intervention was delivered using a Magstim Rapid2 system (Magstim Co., Dyfed, UK) with a double-cone coil. The HF-rTMS was applied over the left SMA located 3–4 centimeters anterior to the leg motor area, for activation of the right tibialis anterior (TA) muscle (anterior to Cz in the international 10–20 EEG system) in the sagittal plane (Hamada et al., 2008, Kim et al., 2018). The stimulation parameters included a 5-second burst of 10 Hz at 90 % rMT, repeated every

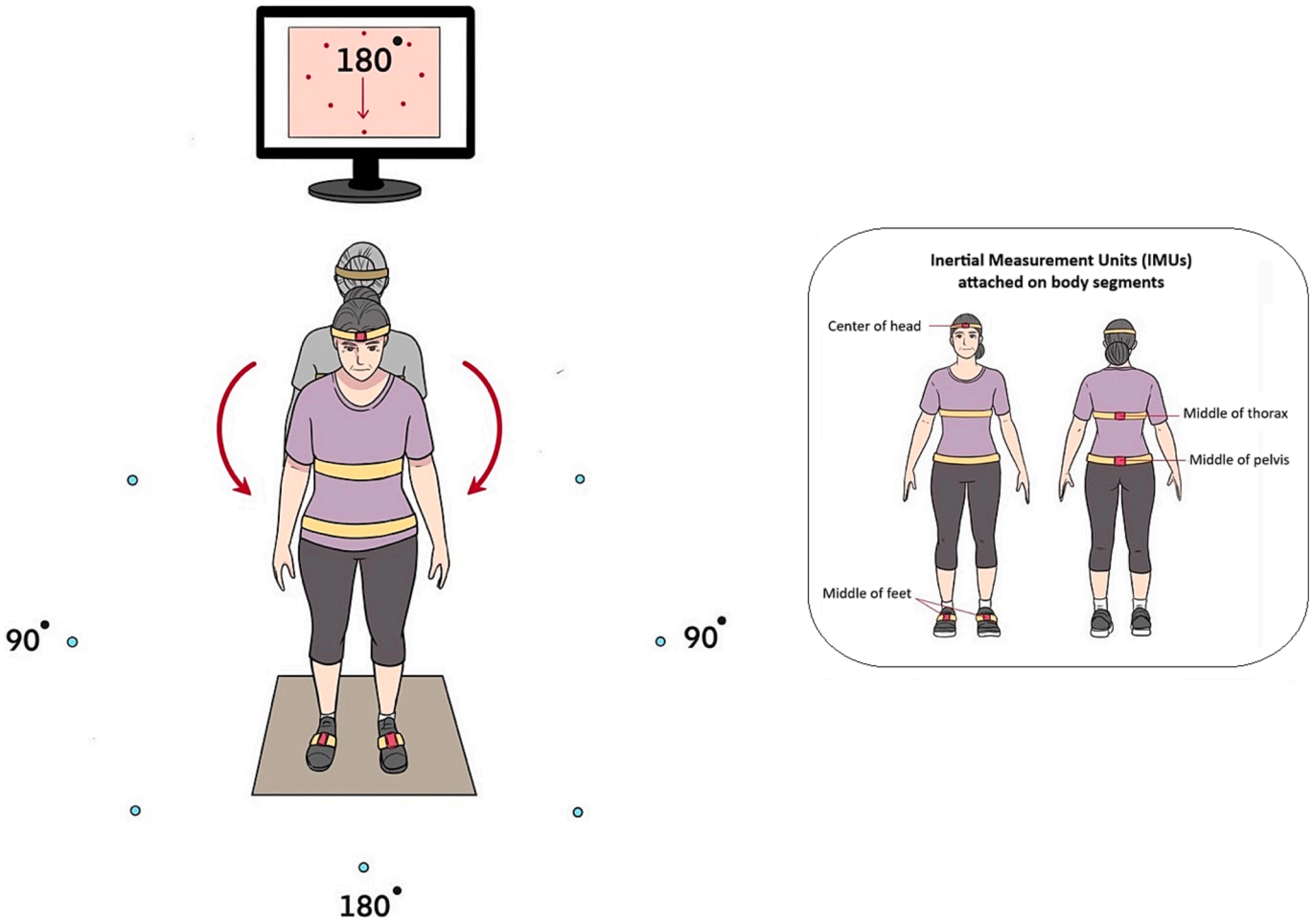

Fig. 3. Turning kinematics and stepping characteristics assessment using Inertial Measurement Units.

minute for 20 min (Mi et al., 2019), totalling 1,000 pulses per session. The rTMS stimulation was administered during the on-medication period.

Participants in both the real rTMS + HB and sham rTMS + HB groups received HF-rTMS stimulation for 10 sessions, as depicted in Fig. 1. For the TMS protocol, the real rTMS + HB group received real HF-rTMS over the left SMA cortex. The stimulation was delivered using a double-cone coil rTMS. In the sham rTMS + HB group, stimulation was applied over the vertex with the coil tilted at a 90-degree angle, using the same frequency and intensity parameters as the real rTMS + HB group to ensure intervention blinding of the participants. This sham HF-rTMS technique followed the sham protocol described in previous studies (Thanakamchokchai et al., 2020b). Following the first rTMS session on the 1st day, participants in both the real rTMS + HB and sham rTMS + HB groups began the home-based exercise program.

2.6. Description of the home-based (HB) exercise program for both real rTMS + HB and sham rTMS + HB groups, along with details of the control group

The home-based exercise program was based on a previously published protocol (Khobkhun et al., 2021a) (details in supplementary material). In brief, the home-based program consisted of the following elements: deep breathing and posture correction (3 repetitions for 5 min), stretching (3 repetitions for 10 min), axial segment rotation training for a total of 30 min (10 repetitions each in supine, side lying, prone lying, sitting, and standing), balance training and task-specific gait and turning training (5 repetitions per side for 15–20 min), with each home-based exercise program session lasting a total of 60–75 min. Each participant in the real rTMS + HB and sham rTMS + HB groups that received the home-based exercise program completed 56 home-based sessions over an 8 weeks period. During rotational movements, participants performed exercises in time with a metronome, which set the speed for each participant. Participants were encouraged to perform each exercise to their maximum potential and focus on perceptual feedback (e.g., how they felt after exerting their maximum effort). To ensure that all participants in the real rTMS + HB and the sham rTMS + HB groups followed the regimen correctly, participants in these groups were instructed to attend the clinic with their caregivers for the baseline assessment. During the session, they were guided through the exercises in a step-by-step manner. They were then provided with a booklet and video for use at home. To monitor adherence, adverse effects, and recording of fall, participants in the real rTMS + HB and sham rTMS + HB groups received a comprehensive exercise program, including a booklet to log adherence, adverse effects, and fall events over an 8-week period, with daily recording sessions. They were also provided with a video for home-based exercises, which they could refer to and perform daily throughout the 8 weeks. Weekly phone calls were used to record and increase the likelihood of adherence.

Participants in the control group were instructed to maintain their usual daily activities and continue their regular PD medication regimen throughout the study. They recorded their activities in a logbook and received weekly calls to assess adherence to the study protocol, without any additional interventions.

3. Statistical analysis

SPSS statistics version 29 (IBM Corporation, Armonk, NY) was used for all statistical procedures. The distribution of all data was tested using Shapiro–Wilk tests and all data found suitable for parametric testing. All data were reported as mean ± SD. A Mixed Model analysis of variance (MM ANOVA) with post hoc pairwise comparisons were performed to assess the effects of two factors: three groups and three assessment time points. Where significant interactions between the groups and time points were seen further repeated measures ANOVA (RM ANOVA) tests were performed to determine the effects of time point within the three groups separately. Any significant main effects seen from the MM ANOVA or RM ANOVA tests were further explored using post hoc pairwise comparisons with Bonferroni correction for multiple comparisons. Partial eta squared (η_p^2) was used to represent the effect size. Statistical significance was set at $p < 0.05$.

4. Results

Forty-eight individuals with PD were recruited for this study, with 16 assigned to each of the 3 groups. However, 3 individuals did not meet the eligibility criteria, leaving 15 participants per group. Six participants (two from each group) were unable to complete the baseline assessments and were withdrawn from the study. In addition, one participant in the control group did not complete the 8-week follow-up. Consequently, data from 13 participants per group were analysed using an intention-to-treat approach, with the last observation carried forward.

Table 1
Participant demographics and one-way ANOVA results for the real repetitive Transcranial Magnetic Stimulation and home-based exercise (real rTMS + HB, n = 13), the sham repetitive Transcranial Magnetic Stimulation and home-based exercise group (sham rTMS + HB, n = 13) and control groups (n = 13).

Demographic	real rTMS + HB (n = 13)	sham rTMS + HB (n = 13)	control (n = 13)	*p*-value*
Age (years, mean ± SD)	66.08 ± 5.45	66.15 ± 4.22	66.31 ± 5.99	0.994
Gender (female/male)	7/6	7/6	7/6	–
Body mass index (kg/m^2, mean ± SD)	24.14 ± 3.33	23.95 ± 4.65	24.02 ± 3.65	0.989
Onset duration of Parkinson's disease (years, mean ± SD)	8.46 ± 4.81	8.38 ± 5.41	8.38 ± 4.77	0.999
Modified Hoehn and Yahr scale (stages ± SD)	2.15 ± 0.47	2.15 ± 0.63	2.19 ± 0.48	0.978
MDS-UPDRS Part III (scores, mean ± SD) at baseline	27.54 ± 11.09	25.00 ± 10.34	27.08 ± 8.88	0.795
Thai Mental State Examination (scores, mean ± SD)	27.23 ± 2.09	27.62 ± 1.80	27.15 ± 1.95	0.813
Underlying disease (n, %)				
– Hypertension	4 (30.8 %)	5 (38.5 %)	2 (15.4 %)	0.550
– Diabetes mellitus	2 (15.4 %)	2 (15.4 %)	1 (7.7 %)	1.000
– Heart	3 (23.1 %)	2 (15.4 %)	2 (15.4 %)	0.233
– Others	3 (23.1 %)	5 (38.5 %)	5 (38.5 %)	0.757
Taking L-DOPA with other medications (n)	13	13	13	N/A
Levodopa equivalent dose (mg/day)	1098.38 ± 329.90	1012.31 ± 274.08	1026.69 ± 287.75	0.735

Abbreviations: real rTMS + HB – the real repetitive Transcranial Magnetic Stimulation and home-based exercise group, sham rTMS + HB – the sham repetitive Transcranial Magnetic Stimulation and home-based exercise group, SD – Standard deviation, MDS-UPDRS Part III – Movement Disorder Society – sponsored revision of the Unified Parkinson's Disease Rating Scale Part III (motor score), n – number, and % – percentage.

* The p-value was calculated using one-way analysis of variance (ANOVA).

Table 1 shows the demographic details of the participants. A one-way ANOVA revealed no significant differences among the three groups ($p > 0.05$) with regard to age, body mass index, PD duration, cognitive ability, stage of PD, MDS-UPDRS Part III (motor score), underlying disease or medical status, and levodopa equivalent dose, which was calculated as described in previous research (Tomlinson et al., 2010).

The results of the MM ANOVA for the three groups across the three assessment time points are shown in Table 2. For variables that showed a significant interaction (indicated by # in the Table 1 and Figs. 4–6) between group and time points, RM ANOVA test were performed to assess the effect of time within each group separately. Further post hoc pairwise comparisons using a Bonferroni correction were conducted and are presented in Table 3. However, for variables where MM ANOVA revealed no significant interaction, post hoc pairwise analyses were performed to examine the main effects of group or time points, as shown in Tables A and B in the supplementary files, respectively.

For clinical outcomes, MM ANOVA tests revealed significant interactions ($p < 0.05$) between groups and time points assessment for the MDS-UPDRS Part III (motor score), the MDS-UPDRS total score, the TUG test, the 10-MWT in fast speed, the FES-I, and the FRT (Table 2, Fig. 4 and Fig. 5). Further analysis using RM ANOVA tests revealed significant main effects of time point assessments in the real rTMS + HB group for the MDS-UPDRS Part III, the MDS-UPDRS total score, the FES-I, and TUG test (Table 3). In the case of the MDS-UPDRS Part III, the MDS-UPDRS total score and the FES-I, the post hoc pairwise comparisons showed a significant decrease ($p < 0.05$) between baseline and the 10 session assessments. For the TUG, the post hoc pairwise comparisons showed a significant decrease ($p < 0.05$) between baseline and the 10 sessions, and between baseline and 8 weeks assessment. (Table 3). In addition, a significant main effect of time points assessment was shown in the sham rTMS + HB group by the RM ANOVA which revealed differences in the MDS-UPDRS Part III, the MDS-UPDRS total score, the FES-I and the FRT (Table 3). Post hoc pairwise comparisons showed a significant decrease ($p < 0.05$) between baseline and the 10 session assessments for the MDS-UPDRS Part III, the MDS-UPDRS total score, and the FES-I. Furthermore, a significant decrease ($p < 0.05$) between baseline and the 10 session assessments, and between baseline and 8 weeks assessments was seen in the TUG and the FRT. For the 10-MWT fast speed, the pot hoc pairwise comparisons showed a significant decrease ($p < 0.05$) between baseline and 8 weeks assessment in the sham rTMS group. RM ANOVA tests also revealed significant main effects of time point assessments in the control group for the MDS-UPDRS Part III and the FRT (Table 3). Further post hoc pairwise comparisons showed a significant increase in the MDS-UPDRS Part III between the 10 session and the 8 weeks assessment and showed a significant decrease in the FRT between baseline and the 8 weeks assessment.

Variables showing no interaction effects were the 10-MWT normal speed, the FOG Questionnaire, and the GRoC (Table 2). However, there was a significant main effect of time in the real TMS + HB for the GRoC, and post hoc pairwise comparisons showed that the GRoC decreased when comparing the 10 session to the 8-week assessments ($p = 0.020$) (Table A in the supplementary files). Finally, there was a significant effect main effect of group for the GRoC at the 10 sessions assessment time point between the real rTMS + HB and the control groups ($p < 0.001$) (Table B in the supplementary files). In terms of FOG phenotypes, most participants suffer from drug-resistant conditions.

For the turning characteristics, the MM ANOVA revealed significant interactions ($p < 0.05$) between group and time points assessment including peak head-thorax angular separation, total step count and average step size (Table 2 and Fig. 6A and 6B). RM ANOVA tests revealed the effect of time point assessments in each group (Table 3). A significant improvement in the real rTMS + HB group was found for the average step size and the post hoc pairwise comparisons showed a

Table 2
Mean and standard deviations (SD) and interaction results between group and time of assessment for clinical outcomes, turning characteristics and cortical outcomes variables which performed by a mixed model analysis of variance (MM ANOVA).

Variables	real rTMS + HB (n = 13)			sham rTMS + HB (n = 13)			control (n = 13)			Main effects	
	Baseline	10 sessions	8 weeks	Baseline	10 sessions	8 weeks	Baseline	10 sessions	8 weeks	Group effect *p*-value (η_p^2)	Time effect *p*-value (η_p^2)
Clinical outcomes											
MDS-UPDRS Part III (score) #	27.54 (11.10)	20.23 (5.67)	22.77 (8.86)	25.00 (10.34)	20.15 (8.91)	21.23 (9.86)	27.08 (8.88)	27.50 (7.14)	30.20 (8.23)	0.257 (0.079)	0.001* (0.212)
MDS-UPDRS total score (score) #	42.31 (15.66)	30.38 (11.43)	35.54 (15.60)	37.54 (15.43)	30.08 (13.07)	30.77 (14.04)	40.54 (11.67)	41.75 (9.82)	42.18 (17.59)	0.258 (0.077)	0.003* (0.169)
Timed Up and Go test (TUG) (s) #	12.14 (4.52)	11.05 (3.52)	11.17 (3.95)	12.86 (4.46)	11.70 (5.13)	10.90 (3.01)	13.58 (4.78)	14.59 (5.80)	13.38 (4.41)	0.484 (0.043)	0.046* (0.089)
10-MWT normal speed (m/s)	0.91 (0.26)	0.93 (0.21)	0.97 (0.25)	0.88 (0.23)	0.97 (0.22)	0.96 (0.28)	0.85 (0.23)	0.85 (0.23)	0.82 (0.22)	0.712 (0.020)	0.274 (0.039)
10-MWT fast speed (m/s) #	1.16 (0.31)	1.17 (0.26)	1.19 (0.26)	1.14 (0.27)	1.19 (0.25)	1.23 (0.31)	1.05 (0.27)	1.07 (0.26)	1.04 (0.27)	0.606 (0.030)	0.571 (0.017)
Freezing of Gait Questionnaire (FOG) (score)	9.77 (6.15)	6.62 (4.05)	7.54 (4.96)	7.46 (6.64)	5.46 (5.24)	5.00 (4.95)	8.54 (5.65)	10.25 (4.77)	9.40 (5.44)	0.208 (0.091)	0.063 (0.080)
Falls Efficacy Scale – International (FES-I) (score) #	28.92 (8.52)	22.38 (4.03)	26.08 (7.11)	26.62 (9.72)	21.23 (6.91)	23.23 (7.19)	28.08 (9.65)	29.75 (9.41)	31.60 (8.53)	0.142 (0.111)	0.007* (0.138)
Functional Reach Test (FRT) (inch) #	7.52 (2.30)	8.47 (1.19)	8.68 (1.62)	6.23 (2.41)	8.17 (1.84)	7.77 (2.72)	7.12 (1.91)	6.23 (2.70)	4.96 (3.12)	0.029* (0.179)	0.133 (0.057)
Global Rating of Change (GRoC) (score)	–	3.15 (0.90)	1.85 (1.91)	–	2.46 (1.66)	1.85 (1.86)	–	0.33 (1.23)	0.18 (1.66)	<0.001* (0.403)	0.052 (0.109)
Turning characteristics											
%Total of event onset latency											
- Head	8.61 (8.48)	3.52 (8.58)	7.60 (9.52)	7.38 (8.72)	6.76 (13.56)	6.51 (9.88)	11.75 (15.29)	8.06 (9.35)	13.72 (15.37)	0.277 (0.075)	0.240 (0.042)
- Thorax	15.81 (9.42)	15.37 (12.12)	12.67 (6.67)	12.61 (10.08)	11.05 (9.55)	9.83 (9.45)	8.98 (10.89)	15.91 (11.59)	15.42 (13.21)	0.386 (0.056)	0.550 (0.018)
- Pelvis	9.30 (11.02)	10.63 (10.09)	9.22 (7.66)	5.89 (6.78)	10.28 (10.72)	10.77 (8.57)	10.48 (19.13)	12.03 (9.48)	5.49 (4.73)	0.912 (0.006)	0.647 (0.012)
- Leading foot	11.76 (8.19)	15.36 (13.51)	13.71 (8.59)	11.12 (9.36)	17.19 (8.05)	14.58 (12.96)	16.55 (18.43)	12.29 (8.89)	18.70 (15.73)	0.604 (0.030)	0.695 (0.011)
- Trailing foot	23.13 (8.37)	27.07 (15.46)	28.60 (9.32)	26.05 (11.35)	31.77 (9.74)	25.12 (11.21)	29.30 (17.07)	25.13 (7.27)	33.26 (15.73)	0.658 (0.025)	0.633 (0.014)
Turning duration (s)	5.60 (3.03)	4.88 (1.57)	4.21 (1.43)	6.61 (2.96)	4.63 (1.90)	4.52 (2.01)	5.63 (1.84)	5.21 (1.93)	7.27 (5.41)	0.452 (0.047)	0.053 (0.091)
Peak head-thorax angular separation (degree) #	59.96 (25.03)	67.92 (21.13)	63.43 (23.46)	44.84 (12.60)	46.81 (12.18)	58.51 (14.03)	47.15 (22.28)	50.60 (35.49)	32.53 (14.38)	0.002* (0.316)	0.408 (0.027)
Peak head velocity (degree/s)	140.39 (36.30)	166.16 (30.37)	159.00 (35.95)	178.83 (51.98)	209.96 (60.25)	199.78 (36.43)	146.65 (37.68)	131.69 (32.34)	129.64 (23.72)	<0.001* (0.403)	0.046* (0.089)
Peak head-pelvis angular separation (degree)	28.05 (11.53)	31.43 (9.96)	36.57 (13.31)	29.02 (12.13)	39.21 (18.64)	38.57 (17.89)	50.89 (60.88)	38.18 (23.82)	32.14 (19.06)	0.779 (0.015)	0.072 (0.077)
Total step count (number) #	3.08 (1.32)	2.92 (1.04)	2.77 (0.83)	3.50 (1.37)	2.73 (0.60)	2.62 (0.79)	3.23 (1.49)	3.13 (1.58)	3.95 (2.66)	0.477 (0.044)	0.185 (0.051)
Average step size (degree) #	41.34 (13.98)	49.33 (12.22)	55.56 (13.39)	38.81 (12.44)	56.20 (11.55)	48.80 (11.68)	47.44 (21.73)	45.88 (15.96)	40.12 (17.44)	0.866 (0.009)	0.026* (0.104)
Cortical outcomes											
Resting motor threshold (rMT) (%)	45.46 (7.95)	47.46 (8.30)	46.38 (8.26)	51.69 (7.11)	52.46 (9.47)	53.54 (9.79)	50.83 (9.66)	51.36 (9.90)	52.78 (8.80)	0.147 (0.113)	0.173 (0.053)
Corticospinal Excitability											
MEP amplitude recorded at 110 % of rMT (μV)	408.20 (312.14)	274.42 (242.16)	279.91 (163.53)	237.17 (204.25)	186.49 (117.63)	210.41 (144.97)	306.84 (319.58)	217.76 (214.97)	220.33 (205.37)	0.085 (0.143)	0.096 (0.076)
MEP amplitude recorded at 120 % of rMT (μV)	694.04 (510.62)	460.00 (261.82)	488.23 (369.87)	444.63 (386.92)	308.34 (195.75)	308.02 (183.98)	435.47 (393.72)	304.44 (180.49)	321.57 (197.08)	0.064 (0.158)	0.030* (0.115)
MEP amplitude recorded	855.17 (519.49)	689.47 (696.63)	760.39 (857.38)	676.36 (824.75)	411.82 (358.51)	389.51 (170.50)	749.46 (465.47)	457.65 (328.21)	359.06 (279.25)	0.149 (0.112)	0.090 (0.079)

(*continued on next page*)

Table 2 (*continued*)

Variables	real rTMS + HB (n = 13)			sham rTMS + HB (n = 13)			control (n = 13)			Main effects	
	Baseline	10 sessions	8 weeks	Baseline	10 sessions	8 weeks	Baseline	10 sessions	8 weeks	Group effect *p*-value (η_p^2)	Time effect *p*-value (η_p^2)
at 130 % of rMT (μV)											
MEP amplitude recorded at 140 % of rMT (μV)	1017.66 (694.83)	990.67 (1007.63)	1013.57 (677.07)	1001.64 (1013.18)	557.34 (424.10)	574.87 (427.44)	1037.31 (638.64)	587.39 (358.16)	576.47 (526.97)	0.210 (0.093)	0.078 (0.081)
Slope Input – Output curve	198.95 (244.55)	237.82 (357.59)	247.32 (240.12)	252.51 (307.35)	121.60 (120.92)	117.49 (111.09)	250.54 (189.90)	112.42 (98.47)	110.59 (99.42)	0.372 (0.060)	0.339 (0.032)
Cortical Inhibition											
Relative Cortical Silent Period (ms)	137.01 (34.54)	144.53 (23.88)	147.37 (39.67)	128.48 (18.85)	130.64 (24.44)	173.94 (92.53)	148.13 (31.17)	148.49 (34.51)	134.50 (25.03)	0.992 (0.001)	0.315 (0.034)
Absolute Cortical Silent Period (ms)	78.77 (31.31)	79.87 (19.23)	94.64 (35.57)	67.78 (18.91)	69.85 (21.84)	116.61 (93.62)	86.30 (29.57)	92.78 (30.46)	80.24 (27.10)	0.975 (0.002)	0.127 (0.067)

Abbreviations: real rTMS + HB – the real repetitive Transcranial Magnetic Stimulation and home-based exercise group, sham rTMS + HB – the sham repetitive Transcranial Magnetic Stimulation and home-based exercise group, SD – Standard deviation, MDS-UPDRS – Movement Disorder Society – sponsored revision of the Unified Parkinson's Disease Rating Scale, 10-MWT – 10-Meter Walk Test, s – second, TUG – Timed Up and Go test, FES-I – Falls Efficacy Scale – International, FRT – Functional Reach Test, m – Meter, μV – Microvolts, ms – millisecond, rMT – Resting motor threshold, and MEP – Motor Evoked Potential.

[#] Indicates a significant interaction ($p < 0.05$) between groups and time points assessment from a mixed model ANOVA (MM ANOVA). For clinical outcomes; the MDS-UPDRS Part III (motor score) ($F_{(2, 33)} = 1.42$, $p = 0.019$, $\eta_p^2 = 0.079$), the MDS-UPDRS total score ($F_{(2, 33)} = 2.81$, $p = 0.042$, $\eta_p^2 = 0.142$), the TUG test ($F_{(2, 33)} = 2.78$, $p = 0.034$, $\eta_p^2 = 0.144$), the 10-MWT in fast speed ($F_{(2, 33)} = 2.61$, $p = 0.044$, $\eta_p^2 = 0.136$), and the FRT ($F_{(2, 33)} = 6.88$, $p < 0.0001$, $\eta_p^2 = 0.277$) and for turning characteristics; peak head-thorax angular separation ($F_{(2, 33)} = 7.61$, $p = 0.002$, $\eta_p^2 = 0.316$), total step count ($F_{(2, 33)} = 3.81$, $p = 0.013$, $\eta_p^2 = 0.187$) and average step size ($F_{(2, 33)} = 4.93$, $p = 0.002$, $\eta_p^2 = 0.230$).

[*] Indicates a significant main effect of groups or time of assessments by a MM ANOVA ($p < 0.05$).

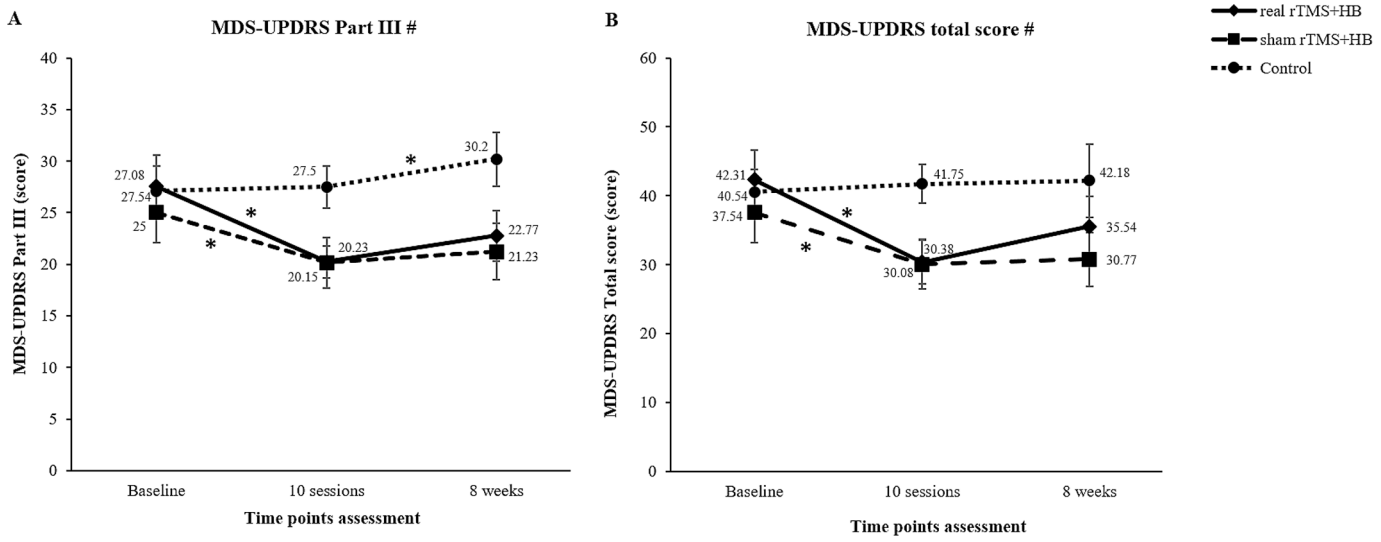

Fig. 4. The mean values and standard errors of the MDS-UPDRS total score and the MDS-UPDRS Part III (motor score) in the real rTMS + HB group (solid line), the sham rTMS + HB group (dashed line), and the control group (dotted line) at baseline, after 10 sessions, and at the 8 weeks follow-up are shown in Fig. 4A and 4B, respectively. # Indicates a significant interaction ($p < 0.05$) between groups and time points assessment from Mixed Model Analysis of Variance, and * indicates the effects of time assessments within each group analysed by a post hoc comparisons from Repeated Measures Analysis of Variance. MDS-UPDRS – Movement Disorder Society – sponsored revision of the Unified Parkinson's Disease Rating Scale.

significant decrease ($p = 0.012$) between baseline and 8 weeks assessment. There was also a significant improvement in the sham rTMS + HB for the peak head-thorax angular separation ($p = 0.013$) between the 10 sessions and the 8 weeks assessment and for the total step count ($p = 0.044$) between baseline and 8 weeks assessment (Table 3). In addition, there was no significant interaction between group and time points assessment for the percentage of event onset latency, peak head velocity and peak head-pelvis angular separation from the MM ANOVA. Solely in the real rTMS + HB group, a further analysis using an RM ANOVA revealed a significant main effect of time for peak head velocity. Post hoc pairwise comparisons showed a significant improvement between baseline and the 10 sessions assessment, and between baseline and the 8 weeks assessment (Table A in supplementary files). Furthermore, post hoc pairwise comparisons from MM ANOVA revealed a significant main effect of the group for each time for the peak thorax-pelvis angular separation ($p = 0.010$) and the peak head velocity ($p < 0.001$) (Table B in supplementary files). At baseline assessment, a significant difference in peak thorax-pelvis angular separation was found between the real rTMS + HB and the control groups. At the 10 sessions assessment, post hoc pairwise comparisons showed that the peak head velocity increased in comparisons between the sham rTMS + HB to the control groups. Finally, at the 8 weeks assessment, a significant main effect group was

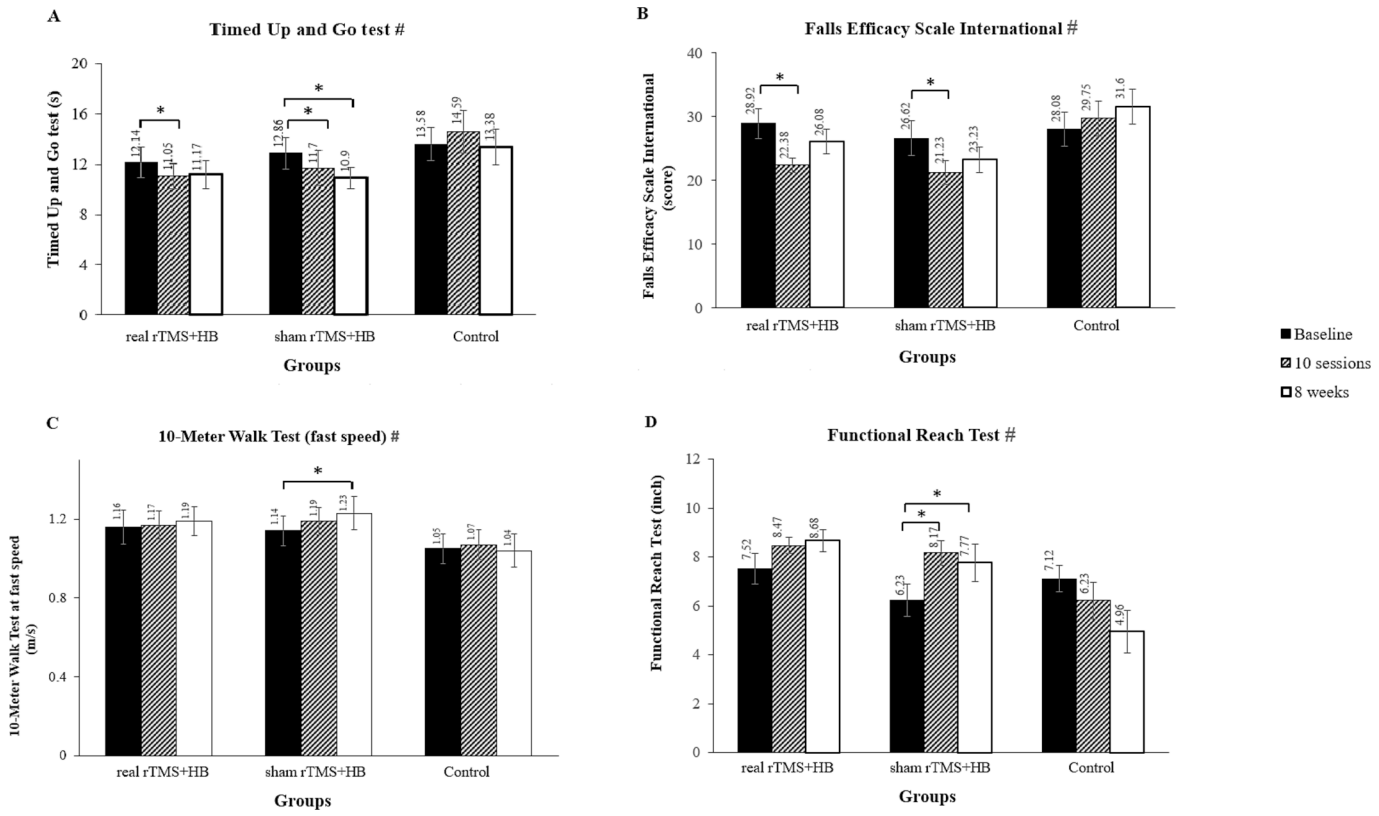

Fig. 5. The mean values and standard errors of the Timed Up and Go test, the Fall Efficacy Scale International, the 10 Meter-Walk Test at fast speed, and the Functional Reach Test of the real rTMS + HB group (black bar), the sham rTMS + HB group (dashed bar), and the control group (white bar) at baseline, 10 sessions and at the 8 weeks follow-up of time points assessment are shown in Fig. 5A, 5B, 5C and 5D, respectively. # Indicates a significant interaction ($p < 0.05$) between groups and time points assessment from Mixed Model Analysis of Variance, and * indicates the effects of time assessments within each group analysed by a post hoc comparisons from Repeated Measures Analysis of Variance.

also found for the peak head velocity increased comparison between the real rTMS + HB and the sham TMS + HB groups ($p = 0.011$) and between the sham rTMS + HB and the control groups ($p < 0.001$).

For the cortical outcomes, MM ANOVA revealed no significant interaction between group and time points assessment for the rMT, MEP amplitude, input–output curve, and CSP duration (Table 2, Fig. 7A-7D). However, the MM ANOVA revealed a significant main effect of time for MEP amplitude recorded at 120 % of rMT in the real rTMS + HB group. Further post hoc pairwise comparisons showed a significant improvement between baseline and the 10 sessions assessment and between baseline and the 8 weeks assessment (Supplementary Tables A and B).

In terms of adherence to the 10 sessions program over 8 weeks, the real rTMS + HB group showed an adherence rate of 82 %, with a standard deviation (SD) of 0.248. The sham rTMS + HB group had a lower adherence rate of 70 %, with an SD of 0.343. Over the 8 weeks, the adherence rate was slightly lower for the real rTMS + HB group at 78 % (SD = 0.219), while the sham rTMS + HB group showed a marginally higher adherence rate of 82 % (SD = 0.224) (Table 4). These results indicate relatively consistent engagement across both groups over the extended period, with the sham group showing a slightly higher adherence. No adverse effects were reported in either the real rTMS + HB or sham rTMS + HB groups. One instance of falling was reported in the control group. Three participants from the real rTMS + HB group reported that, both they and their caregivers were able to engage in activities together, such as walking around their village, doing housework, and traveling outside Bangkok. Additionally, five participants in the real TMS + HB group and six participants in the sham rTMS + HB group reported experiencing easier movement, reduced stiffness, and improved mobility during the 8 weeks. While participants in the control group were encouraged to record their activities during the study, most performed exercises independently or engaged in regular daily activities, such as housework, walking around their village for less than 30 min, or traveling either alone or with family.

5. Discussion

To the best of our knowledge, this is the first study to investigate the effects of combining rTMS with a home-based exercise program with the aim to improve locomotion in individuals with mild to moderate PD. Our findings indicate that the improvements in clinical outcomes, gait, and turning observed in both the real and sham rTMS + HB groups suggest the primary efficacy of the home-based exercise program. Although real rTMS induced measurable neurophysiological changes, these did not translate into greater functional improvements compared to sham stimulation. This indicates the need for further exploration of the neuromodulatory role of HF-rTMS over the SMA, particularly regarding its optimal parameters and long-term impact in PD.

Significant interactions between group and time point assessments were observed for the MDS-UPDRS Part III, MDS-UPDRS total score, TUG, FRT, and 10-MWT at fast speed. Specifically, the combination of real rTMS and home-based exercise showed benefits on the FRT compared to the control group after 10 sessions and at 8 weeks. The sham rTMS group also demonstrated significant improvements in FRT at 8 weeks compared to the control group. Additionally, the GRoC showed a significant difference at 10 sessions between the real rTMS group and the control group. However, no significant differences were found in the FOG Questionnaire or 10-MWT at normal speed following the real rTMS + HB compared to sham rTMS + HB or control groups. Despite non-significant differences, the FOG score in the real rTMS + HB and the sham rTMS + HB groups tended to decrease compared to baseline at 10

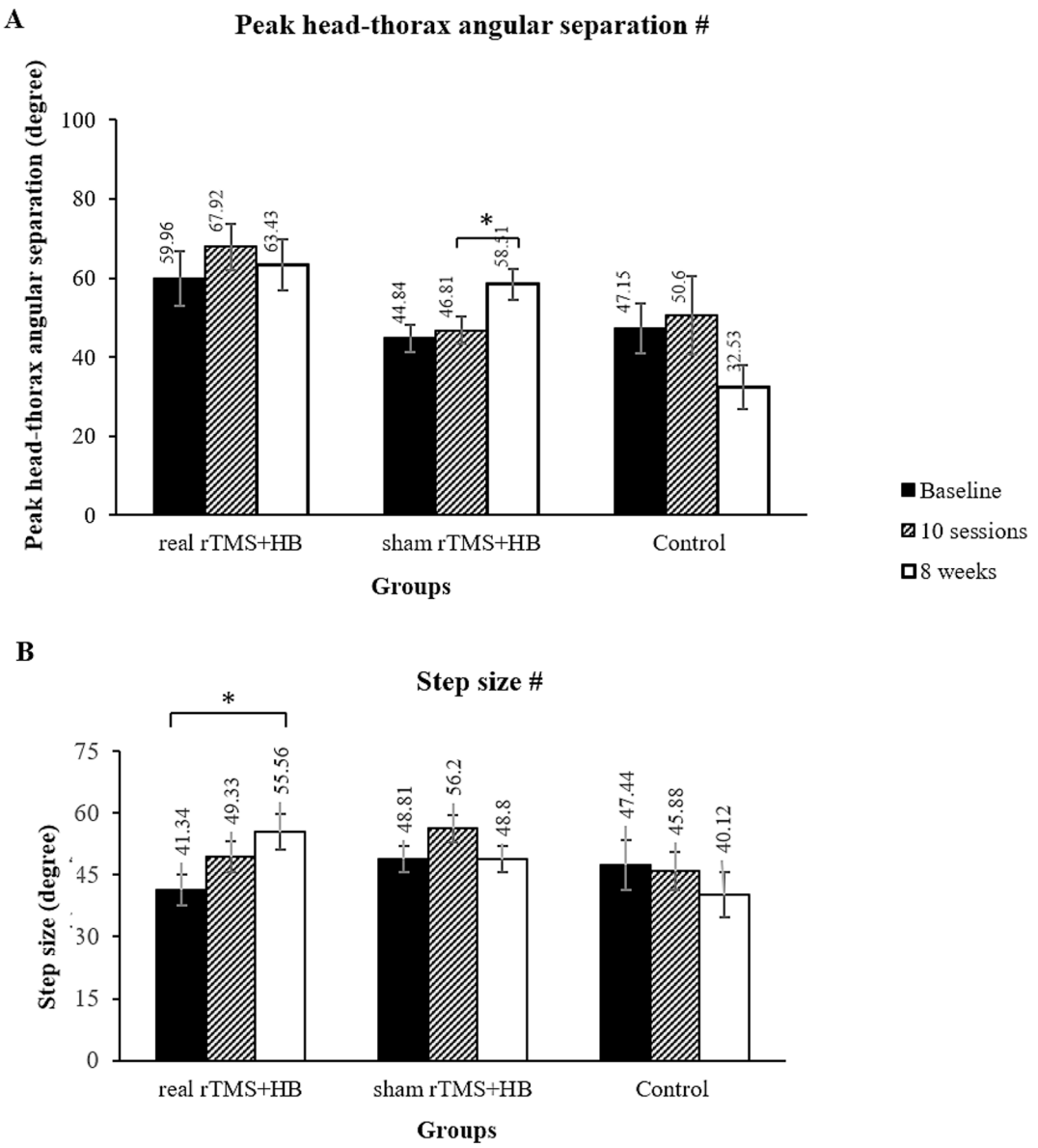

Fig. 6. The mean values and standard errors of the peak head-thorax angular separation, and average step size of the real rTMS + HB group (black bar), the sham rTMS + HB group (dashed bar), and the control group (white) at baseline, 10 sessions and 8 weeks followed-up of time points assessment as shown in Fig. 6A and 6B, respectively. # Indicates a significant interaction ($p < 0.05$) between groups and time points assessment from Mixed Model Analysis of Variance, and * indicates the effects of time assessments within each group analysed by a post hoc comparisons from Repeated Measures Analysis of Variance.

sessions and 8 weeks, unlike the control group, which showed an increase. Consistent with a previous study (Mi et al., 2019), our combination of HF-rTMS over the SMA with home-based exercise significantly improved clinical outcomes, including the MDS-UPDRS Part III, MDS-UPDRS total score, and FES-I. In addition, functional performance, including TUG and average step size, were significantly improved after continuous home-based exercise for up to 8 weeks.

The real HF-rTMS combined with home-based exercise also significantly improved peak head-thorax angular separation in turning characteristics compared to both sham rTMS + HB and control groups at 10 sessions and 8 weeks. Peak head velocity also significantly improved after 10 sessions and 8 weeks. These improvements suggest that home-based exercise is beneficial for individuals with PD, with the priming HF-rTMS potentially enhancing the effects of home-based exercise on turning characteristics. This is in contrast to a previous study where no significant differences were observed in peak head-thorax and peak head-pelvis angular separations (Khobkhun et al., 2021a).

When considering the neurophysiological responses, only the real rTMS + HB group showed a decrease in peak-to-peak MEP amplitude (MEP amplitude recorded at 120 % of rMT) when compared to baseline measurements and after 10 sessions or 8 weeks follow-up. While this may reflect modulation of cortical excitability, it did not correspond with superior clinical outcomes, turning kinematics, or gait performance relative to the sham rTMS + HB group. This dissociation suggests that changes in cortical excitability alone may not be sufficient to drive functional improvements in PD within the parameters of this study. Furthermore, this finding contrasts with previous research reporting a non-significant increase in MEP amplitude following SMA stimulation (Lee et al., 2014), highlighting variability in neurophysiological responses.

The observed reduction in cortical excitability following real rTMS stimulation over the SMA, despite the absence of corresponding improvements in clinical gait parameters, warrants cautious interpretation. A critical methodological consideration is that the rTMS in our study was delivered using a double cone coil, which is known to stimulate deeper cortical structures beyond the SMA, such as the cingulate

Table 3
Post hoc comparisons from Repeated Measures Analysis of Variance (RM ANOVA) for the **effects of time assessments within each group** for the variables that **showed a significant interaction** from Mixed model Analysis of Variance (MM ANOVA).

Groups	Variables	Time point of assessments	Mean Diff (SE)	*p*-Value	CI of Diffs	
					Lower Bound	Upper Bound
real rTMS + HB (n = 13)	MDS-UPDRS Part III (score)	Baseline vs 10 sessions	7.308 (2.055)	0.012*	1.596	13.019
		Baseline vs 8 weeks	4.769 (1.919)	0.086	−0.564	10.102
		10 sessions vs 8 weeks	−2.538 (1.435)	0.307	−6.527	1.450
	MDS-UPDRS total score (score)	Baseline vs 10 sessions	11.923 (2.427)	0.001*	5.177	18.669
		Baseline vs 8 weeks	6.769 (2.649)	0.076	−0.592	14.131
		10 sessions vs 8 weeks	−5.154 (1.874)	0.053	−10.362	0.054
	Falls Efficacy Scale – International (score)	Baseline vs 10 sessions	6.538 (2.059)	0.014*	0.816	12.261
		Baseline vs 8 weeks	2.846 (1.632)	0.320	−1.691	7.383
		10 sessions vs 8 weeks	−3.692 (1.774)	0.178	−8.622	1.238
	Timed Up and Go test (s)	Baseline vs 10 sessions	1.095 (0.566)	0.031*	−0.479	2.670
		Baseline vs 8 weeks	0.976 (0.393)	0.019*	0.012	2.069
		10 sessions vs 8 weeks	−0.119 (0.389)	1.000	−1.202	0.963
	Average step size (degree)	Baseline vs 10 sessions	−7.989 (5.174)	0.445	–22.369	6.391
		Baseline vs 8 weeks	−14.217 (3.993)	0.012*	−25.314	−3.119
		10 sessions vs 8 weeks	−6.227 (3.706)	0.356	−16.528	4.073
sham rTMS + HB (n = 13)	MDS-UPDRS Part III (score)	Baseline vs 10 sessions	4.846 (1.694)	0.043*	0.138	9.555
		Baseline vs 8 weeks	3.769 (2.167)	0.322	−2.253	9.791
		10 sessions vs 8 weeks	−1.077 (0.909)	0.777	−3.604	1.450
	MDS-UPDRS total score (score)	Baseline vs 10 sessions	7.462 (2.071)	0.011*	1.705	13.218
		Baseline vs 8 weeks	6.769 (2.540)	0.062	−0.290	13.829
		10 sessions vs 8 weeks	−0.692 (1.313)	1.000	−4.341	2.956
	Falls Efficacy Scale – International (score)	Baseline vs 10 sessions	5.385 (1.852)	0.019*	0.237	10.532
		Baseline vs 8 weeks	3.385 (1.546)	0.147	−0.914	7.683
		10 sessions vs 8 weeks	−2.000 (1.281)	0.433	−5.561	1.561
	Timed Up and Go test (s)	Baseline vs 10 sessions	1.160 (0.417)	0.019*	0.001	2.320
		Baseline vs 8 weeks	1.957 (0.663)	0.016*	0.114	3.800
		10 sessions vs 8 weeks	0.797 (0.857)	1.000	−1.585	3.178
	Functional Reach Test (inch)	Baseline vs 10 sessions	−1.941 (0.371)	<0.001*	−2.972	−0.911
		Baseline vs 8 weeks	−1.542 (0.392)	0.006*	−2.632	−0.453
		10 sessions vs 8 weeks	0.399 (0.358)	0.863	−0.597	1.395
	10-MWT fast speed (m/s)	Baseline vs 10 sessions	−0.042 (0.018)	0.118	−0.093	0.008
		Baseline vs 8 weeks	−0.088 (0.030)	0.038*	−0.172	−0.005
		10 sessions vs 8 weeks	−0.046 (0.034)	0.616	−0.142	0.050
	Peak head-thorax angular separation (degree)	Baseline vs 10 sessions	−1.968 (4.265)	1.000	−13.821	9.886
		Baseline vs 8 weeks	−13.665 (5.544)	0.089	−29.076	1.746
		10 sessions vs 8 weeks	−11.697 (3.327)	0.013*	−20.943	−2.451
	Total step count (number)	Baseline vs 10 sessions	0.769 (0.318)	0.098	−0.116	1.654
		Baseline vs 8 weeks	0.885 (0.354)	0.014*	0.100	1.869
		10 sessions vs 8 weeks	0.115 (0.180)	1.000	−0.617	0.386
control (n = 13)	MDS-UPDRS Part III (score)	Baseline vs 10 sessions	0.300 (1.660)	1.000	−4.570	5.170
		Baseline vs 8 weeks	−3.200 (1.340)	0.122	−7.131	0.731
		10 sessions vs 8 weeks	−3.500 (1.293)	0.017*	−7.293	−0.003
	Functional Reach Test (inch)	Baseline vs 10 sessions	0.886 (0.503)	0.311	−0.512	2.285
		Baseline vs 8 weeks	2.156 (0.933)	0.018*	0.004	4.750
		10 sessions vs 8 weeks	1.270 (0.805)	0.422	−0.967	3.506

Abbreviations: real TMS + HB – the real repetitive Transcranial Magnetic Stimulation and home-based exercise group, sham TMS + HB – the sham repetitive Transcranial Magnetic Stimulation and home-based exercise group, SD – Standard deviation, MDS-UPDRS – Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale, s – second, 10-MWT – 10-Meter Walk Test, and m – Meter.
* Indicates a significant difference ($p < 0.05$). Diff = Difference, CI = Confidence Intervals.

cortex. Therefore, we cannot exclude the possibility that the modulation of cortical excitability observed in our study may have resulted, at least partially, from incidental activation of these adjacent or deeper brain areas, rather than specific SMA stimulation alone.

To date, there are limited studies that have reported neurophysiological outcomes, such as cortical excitability measured by MEP amplitude, following SMA stimulation (Kim et al., 2019, Lee et al., 2014), as most have focused primarily on clinical symptoms and motor function (Kim et al., 2018, Kim et al., 2019, Mi et al., 2019, Niemrungruang et al., 2024). Previous evidence has shown no significant changes in MEP amplitude after SMA stimulation in individuals with PD and FOG (Lee et al., 2014). However, in the same study, stimulation of the primary motor cortex or dorsolateral prefrontal cortex resulted in significant increases in MEP amplitude after rTMS (Lee et al., 2014). Future studies should incorporate precise targeting and neuroimaging techniques to more accurately characterize and isolate the cortical regions activated by rTMS and clarify their direct functional implications in PD.

The pathophysiological mechanism of FOG in PD has been associated with reduced SMA activity, likely due to reduced positive efferent feedback from the basal ganglia-thalamocortical pathway, as evidenced by imaging studies (Kim et al., 2018, Kim et al., 2019). Interestingly, according to the records of our neurology team, the FOG experienced by most participants in this study was drug-resistant. A previous study showed that individuals with PD and drug-resistant FOG exhibit corticomotor hyperexcitability, characterized by a lower resting motor threshold and decreased intracortical inhibition, in comparison to non-disabled adults (Lee et al., 2020). This hyperexcitability may represent a compensatory mechanism for impaired function of basal ganglia (Lee et al., 2020). Given this hyperexcitability, HF-rTMS over the SMA might

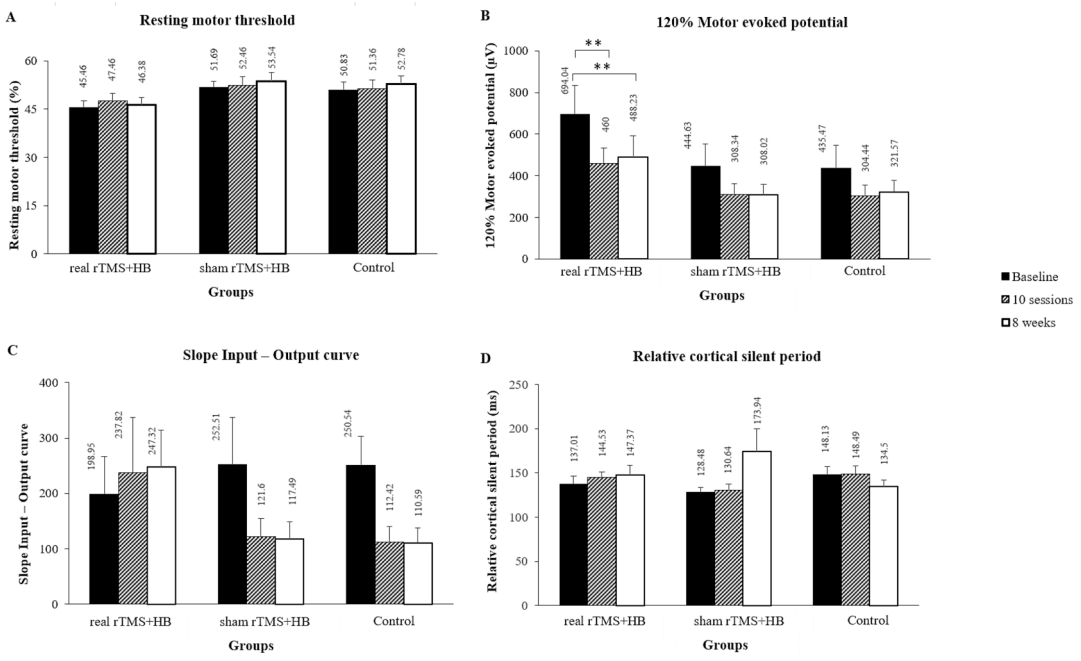

Fig. 7. The mean values and standard errors of the cortical variables of the real rTMS + HB group (black bar), the sham rTMS + HB group (dashed bar), and the control group (white) at baseline, 10 sessions and 8 weeks followed-up of time points assessment are shown Fig. 7A, 7B, 7C and 7D, respectively. ** indicates no significant interaction between groups and time points assessment from Mixed Model Analysis of Variance (MM ANOVA) but there was a significant main effect of time analysed by the post hoc comparisons from MM ANOVA.

Table 4
Participant adherence outcomes over 8-week period.

Outcomes	real rTMS + HB (n = 13)	sham rTMS + HB (n=13)	control (n=13)
Performing home-based exercise (% (SD))			
- 10 sessions	82 (0.248)	78 (0.219)	–
- 8 weeks	70 (0.343)	82 (0.224)	–
Adverse event effect (%)	0	0	0
Falling rate	0	0	1

Abbreviations: real rTMS + HB – the real repetitive Transcranial Magnetic Stimulation and home-based exercise, sham rTMS + HB – the sham repetitive Transcranial Magnetic Stimulation and home-based exercise group, % – percentage, and SD – standard deviation.

modulate corticomotor excitability by reducing excessive activity and restoring network balance. This is supported by a systematic review and *meta*-analysis which recommended HF-rTMS for individuals with PD and FOG due to its potential to modulate motor circuits (Kim et al., 2019). However, as FOG was not an inclusion criterion in this study and not all participants exhibited FOG, interpretations linking SMA stimulation to FOG-specific mechanisms remain speculative.

The non-significant changes in CSP duration and slope I/O curve observed in this study might be due to differences in dopamine (DA) release induced by HF-rTMS over M1 or dorsolateral prefrontal cortex (Cho and Strafella, 2009, Strafella et al., 2005, Strafella et al., 2001, Thanakamchokchai et al., 2020a, Thanakamchokchai et al., 2020b). Although the DA release is known to affect cortical inhibition and CSP duration (Baumer et al., 2009, Lewitt, 2008, Thanakamchokchai et al., 2020b), our study did not find significant differences in CSP duration or I/O curve among groups, though the slope I/O curve showed an increasing trend in the real rTMS + HB group, and the CSP duration was prolonged in both the real rTMS + HB group and the sham rTMS + HB group.

Despite the non-significant changes in cortical outcomes for the sham rTMS in combination with HB, significant improvements in clinical outcomes and turning characteristics were observed. This highlights the potential of home-based exercise as a beneficial adjunct to treatment for improvement in mobility in individuals with PD. Consistent with previous studies, targeted home-based exercise programs have been shown to improve gait and turning characteristics in individuals with PD by reducing en bloc turning and enhancing segmental coordination during turns (Khobkhun et al., 2021a, Khobkhun et al., 2021b). Another study highlighted that task-specific movement training could promote more efficient turning strategies, leading to improved turning characteristics (Khobkhun et al., 2022a). However, those previous studies did not evaluate neurophysiological outcomes. Our findings support the idea that combining exercise with priming interventions like HF-rTMS may enhance cortical adaptation, though further validation is required. In contrast, participants in the control group, who received only medication and routine care, clinical outcomes and mobility worsened over time in comparison to baseline. This emphasizes the importance of active rehabilitative strategies in maintaining mobility and independence in individuals with PD. Although the cortical effects of HF-rTMS were not mirrored in functional outcomes, the neurophysiological findings offer insights into the underlying brain mechanisms.

There are limitations to this study. Firstly, the reduction in sample size due to participant withdrawals and exclusions. Only 13 participants per group (39 participants in total) were included in the final analysis. The final sample size was reduced from the original planned number, which limited the statistical power and may affect the generalizability of the findings. Future studies are recommended to replicate these findings using larger sample sizes to provide more definitive conclusions. Secondly, the home-based exercise was used as a supplementary treatment to support HF-rTMS, which may introduce a measure of subjectivity in adherence (Khobkhun et al., 2021a, Khobkhun et al., 2021b). Therefore, future studies should aim to replicate this protocol using objective measures of exercise adherence. Lastly, the combined intervention and measurement sessions were conducted in the “ON” state, limiting the generalizability of findings as a potential add-on therapy. Future studies

should investigate and compare the effects of this combined intervention in the "OFF" state.

6. Conclusion

This study investigated the effects of combining rTMS with home-based exercise over 10 sessions and to examine the effects on locomotion over an 8-week period in individuals with PD. The findings demonstrated that a structured home-based exercise program effectively improves locomotion and clinical outcomes in individuals with PD. While high-frequency rTMS may influence cortical excitability, it did not confer additional functional benefits beyond exercise alone. These findings underline the importance and efficacy of home-based exercise programs and highlights the need to further explore the potential neurophysiological benefits of rTMS.

CRediT authorship contribution statement

Jenjira Thanakamchokchai: Conceptualization, Writing – original draft, Writing – review & editing, Methodology, Investigation, Formal analysis. **Amornpan Ajjimaporn:** Supervision, Writing – review & editing, Conceptualization, Data curation. **Jim Richards:** Writing – review & editing, Funding acquisition, Conceptualization, Methodology. **Sutang Tantanavivat:** Investigation, Data curation. **Paulo Roberto Pereira Santiago:** Writing – review & editing, Funding acquisition, Conceptualization. **Papatsorn Ramyarangsi:** Investigation, Data curation. **Prachaya Srivanitchapoom:** Methodology, Investigation. **Weerawat Saengphatrachai:** Methodology, Investigation. **Yuvadee Pitakpatapee:** Methodology, Investigation. **Jarugool Tretriluxana:** Conceptualization, Supervision. **Fuengfa Khobkhun:** Writing – original draft, Writing – review & editing, Methodology, Formal analysis, Conceptualization, Investigation, Data curation, Funding acquisition.

Funding

This research project is supported by Mahidol University (MU's Strategic Research Fund: 2023 (MU-SRF-RS-07A/66)).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Dr. Phunsuk Kanta for his support of the XSENS data analysis. Thank you for a three-way collaboration between experts in Thailand, Brazil and the UK. The authors would also like to thank all participants for their involvement in this study. Furthermore, the authors wish to thank the staff of the Faculty of Physical Therapy and acknowledge the financial support provided by Mahidol University, which facilitated the completion of this project.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.2110957.

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