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Height-dependent variation in corticospinal excitability modulation after active but not sham intermittent theta burst stimulation

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ABSTRACT

Poor reproducibility and high inter-individual variability in responses to intermittent theta burst stimulation (iTBS) of the human motor cortex (M1) are matters of concern. Here we recruited 17 healthy young adults in a randomized, sham-controlled, crossover study. Transcranial magnetic stimulation (TMS)-elicited motor evoked potentials (MEPs) were measured pre-iTBS (T0) and post-iTBS at 4–7 (T1), 9–12 (T2), 17–20 (T3), and 27–30 minutes (T4) from the right first dorsal interosseous muscle. MEP grand average (MEPGA) was defined as the mean of the normalized-to-baseline MEPs at all timepoints post-iTBS. As secondary objectives, we measured blood pressure, heart rate, and capillary blood glucose pre-iTBS, and at 0 and 30 minutes post-iTBS. The TMSens_Q structured questionnaire was filled out at the end of each session. Two-way repeated ANOVA did not show a significant TIME×INTERVENTION interaction effect on MEP amplitude, MEP latency, blood pressure, heart rate, and blood glucose ($p > 0.05$). Sleepiness was the most reported TMSens_Q sensation (82.3 %) in both groups. Surprisingly, the subjects' height negatively correlated with the normalized MEP amplitudes at T3 ($r = -0.65$, $p = 0.005$), T4 ($r = -0.66$, $p = 0.004$), and MEPGA ($r = -0.68$, $p = 0.003$), with a trend correlation at T1 ($r = -0.46$, $p = 0.062$) and T2 ($r = -0.46$, $p = 0.065$) in the active but not sham group. In view of this, we urge future studies to delve deeper into the influence of height on neuroplasticity induction of the M1 representation of peripheral muscles. In the end, we highlight unique methodological considerations in our study protocol and future recommendations for M1-iTBS studies.

1. Introduction

Transcranial magnetic stimulation (TMS) is an invaluable tool to study the human brain non-invasively. Theta-burst stimulation (TBS) is a patterned TMS protocol that can modulate cortical excitability beyond the stimulation period. Neuromodulatory effects of the TBS protocol over the primary motor cortex (M1) can be quantified by comparing the peak-to-peak amplitude of TMS-elicited motor evoked potentials (MEPs) from a peripheral small hand muscle before vs. after TBS (Huang et al., 2005). This MEP wave consists of both cortical- and spinal-segmental contributions, which can be difficult to dissociate (Bestmann and Krakauer, 2015). The MEP amplitude is conventionally used as an outcome measure of corticospinal excitability, while MEP latency determines the conduction time taken for intracortical processing, corticofugal conduction, spinal processing, and neuromuscular transmission (Bestmann and Krakauer, 2015; Groppa et al., 2012).

As demonstrated in the pioneering study of Huang et al., intermittent TBS (iTBS) protocol, comprising 50 Hz pulse-triplets repeated every 200 ms in a 2-second on, 8-second off pattern for 192 s, enhanced corticospinal excitability for the subsequent 30 minutes in comparison to baseline excitability. Whereas continuous TBS (cTBS) protocol, comprising 50 Hz pulse-triplets repeated every 200 ms for 40 seconds, suppressed corticospinal excitability for 60 minutes in comparison to baseline excitability (Huang et al., 2005). This duality of after-effects has been considered ever since as proof of effectiveness of the iTBS and cTBS protocols in increasing or decreasing corticospinal excitability,

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respectively (Chung et al., 2016; Corp et al., 2020; Suppa et al., 2016; Wischnewski and Schutter, 2015). Surprisingly, however, the available literature on M1-iTBS has been mostly derived from studies with pretest-posttest designs, rather than sham-controlled studies, and from protocols that measured MEP amplitude with monophasic pulses, despite the biphasic waveform configuration of the TBS protocols and the different recruited circuits inside the brain and descending corticospinal volleys by both waveforms (Di Lazzaro et al., 2001; Sommer et al., 2006; Sommer et al., 2018). Furthermore, M1-iTBS studies have mainly reported the MEP amplitude as an outcome measure of corticospinal excitability, without proper documentation of the MEP latency changes, despite their covariation (Vallence et al., 2023).

Of concern, accumulating well-conducted, sham-controlled studies have shown no statistical significance of the interaction effect between iTBS (with factors: active and sham) with the time factor on corticospinal excitability as indicated by a non-significant MEP amplitude modulation over time compared to sham (Boucher et al., 2021; Magnuson et al., 2023; McCalley et al., 2021; Mittal et al., 2021; Perellón-Alfonso et al., 2018; Schilberg et al., 2017). This, in turn, calls into question the robust effectiveness of the iTBS protocol in modulating corticospinal excitability compared to sham stimulation. Therefore, the first aim of this study was to add another line of evidence to this debate from a different ethnic and geographic perspective.

On the other hand, anecdotal evidence from transcranial direct current stimulation (tDCS), single-pulse TMS, and conventional repetitive TMS studies has demonstrated remote effects of the M1 stimulation on blood pressure and heart rate (Chantigian et al., 2021; Lee et al., 2023; Schmausser et al., 2022), potentially due to the complex interconnection between M1 and the central autonomic network (CAN) (Beissner et al., 2013; Valenza et al., 2019). Furthermore, it was once hypothesized that delivering TMS to the brain might be a novel strategy to treat arterial hypertension (Cogiamanian et al., 2010). Another remote effect of the M1 stimulation was reported after delivering anodal tDCS to the left M1, which led to a significant drop in blood glucose for several minutes after stimulation compared to sham (Kistenmacher et al., 2017). The authors reasoned that the enhanced cortical excitation post-tDCS increased glucose uptake by cerebral neurons and astrocytes in an insulin-independent manner to compensate for the brain's energetic needs upon stimulation. This assumption was supported by a parallel increase in cerebral energy metabolism as shown through ^{31}phosphorus magnetic resonance spectroscopy imaging (Kistenmacher et al., 2017; Wardzinski et al., 2019). However, the remote effects of M1-iTBS on cardiovascular response and blood glucose remain unexplored.

To that end, the primary objective of this study was to explore whether M1-iTBS could modulate corticospinal excitability, as indexed by MEP amplitude and latency, compared to sham stimulation in a Malaysian population. As secondary objectives, we aimed to determine the tolerability of M1-iTBS, using the newly developed TMSens_Q questionnaire (Giustiniani et al., 2022), and its efficacy on cardiovascular response and blood glucose compared to sham stimulation.

2. Material and methods

2.1. Study design and protocol registration

This was a randomized, single-blind, sham-controlled, crossover study in accordance with the CONSORT 2010 extension to crossover designs (Dwan et al., 2019). The crossover study design has been recommended in TMS studies as it significantly reduces the inter-individual variability in responses, hence every individual serves as his or her own control (Guerra et al., 2020; Stoney and Johnson, 2018). This in turn allows the detection of smaller effect sizes with reduced sample size and reduces the variation in nonspecific (nontreatment-related) factors (Stoney and Johnson, 2018).

The study was conducted in the neurophysiology laboratory at Hospital Sultan Abdul Aziz Shah of University Putra Malaysia. Study procedures conformed to the Declaration of Helsinki, and ethical approval was obtained from the local Institutional Review Board, approval number JKEUPM-2023–674. The study protocol was preregistered at ClinicalTrials.gov, ID: NCT06043076, and deidentified raw datasets are freely available on the Open Science Framework repository at https://doi.org/10.17605/OSF.IO/VRNC4.

2.2. Subjects

2.2.1. Sample size

G*power (version 3.1.9.4) software was used to calculate the sample size as ANOVA: repeated measures, within factors (Faul et al., 2007). According to a former meta-analysis, the iTBS protocol was found to increase MEP peak-to-peak amplitude with a mean maximum potentiation of ≈ 35 % (Wischnewski and Schutter, 2015). Therefore, considering an effect size of $f = 0.35$, an $\alpha = 0.05$, a power $(1 - \beta) = 0.9$, and five repeated measures, a minimum sample size of 14 was calculated. As a result, we recruited 18 participants to account for potential drop-out or unmeasurable data.

2.2.2. Selection criteria

Several confounding factors reported in the literature were considered in the following selection criteria to minimize confounding and improve homogeneity of the sample. Inclusion criteria were healthy young adults (18–35 years old) (Corp et al., 2020; Corp et al., 2021), right-handed according to the Edinburgh Handedness Questionnaire (Oldfield, 1971), and fully vaccinated against COVID-19. Exclusion criteria were subjects with contraindications to TMS based on the screening 13-item questionnaire (Rossi et al., 2011), highly active subjects, defined as performing > 150 minutes per day of moderate-to-vigorous aerobic activity on at least 5 days per week (Cirillo et al., 2009; Craig et al., 2003), obese, defined as having a Body Mass Index (BMI) ≥ 30 kg/m2 (Sui et al., 2020), smokers (Lang et al., 2008), and active or previous lab-confirmed COVID-19 with long symptoms (Manganotti et al., 2023; Ortelli et al., 2022).

2.2.3. Visits and instructions

The study involved 3 visits to the lab. Visit 1 was for screening and obtaining written informed consent. Subjects were asked to fill out three short questionnaires: the Oldfield handedness questionnaire, the international physical activity questionnaire, and the 13-item questionnaire for TMS safety. The body height and weight were measured using standardized methods, and BMI was calculated. Subjects were offered a short mock experiment to familiarize themselves with the setting and TMS sensations. Eventually, all eligible subjects signed an informed consent before enrolment. Visits 2 and 3 involved two experimental conditions that each took a ~ 1–1.5 hour visit to the lab, one week apart to avoid any carry-over effects (Fried et al., 2017). Experiments in visits 2 and 3 were performed at the same time of day (± 2 h) in the afternoon for each participant. This was reasoned to minimize the influence of circadian cortisol variations on M1 plasticity (Guerra et al., 2020; Sale et al., 2008). Participants were asked to refrain from strenuous exercise, alcohol and caffeine consumption 24 hr before the testing session, get a night sleep ≥ 6 hr, and arrive at the lab in the afternoon (Pellegrini et al., 2020). None of the participants were under medications known to influence cortical excitability and plasticity (Sohn et al., 2024; Ziemann, 2004; Ziemann et al., 2015).

2.2.4. Randomization and blinding

Participants (n = 18) were randomized to the sequence of active and sham interventions in their both visits with an online random number generator at https://www.randomizer.org/. The study design was single-blinded, i.e., only participants were masked to the intervention. To test the blinding success, subjects were asked at the end of each session if they thought that they had undergone an active or sham

stimulation in that session (Flanagan et al., 2019).

2.3. Transcranial magnetic stimulation (TMS)

2.3.1. Single pulse TMS

All experiments were performed in the afternoon between 11 am and 4 p.m. Participants were seated in a comfortable motorized Lemi® chair with headrest and armrests. Head position was fixed through a cheek-rest attachment of the chair. Room temperature was maintained at 18–20° at all times. Electromyography (EMG) activity was recorded from the right first dorsal interosseous (FDI) muscle using disposable pre-gelled Ag-AgCl surface electrodes (P/N 019–435300, Natus, USA). These electrodes were attached to a reusable alligator-clip lead wire (P/N 117–401900, Natus, USA) and connected to an 8-channel amplifier (AT2 +6, Natus, USA). Participants were seated without visual access to the TMS and EMG equipment display. After cleansing the skin with alcohol swabs, the active/negative EMG electrode was placed on the skin overlying the FDI belly, while the reference/positive electrode was placed on the metacarpophalangeal joint of the index finger, and the ground electrode was placed on the ulnar styloid process of the wrist. We asked the participants to relax their FDI muscle during all measurements. Raw EMG signals were amplified (AT2 +6, Natus, USA), band-pass filtered between 1 Hz to 10 kHz as recommended (Groppa et al., 2012; Zschorlich et al., 2021), digitized at 48 kHz (Nicolet EDX, Natus, USA), and stored on the laboratory computer for offline analysis (Synergy EDX software, version 22.4.1.123, Natus, USA). This software algorithm can automatically score the peak-to-peak amplitude and onset latency of the MEP waves. All participants were offered earplugs to decrease the noise level by the TMS coil as per safety guidelines (Rossi et al., 2009; Rossi et al., 2021). All pulses were delivered as biphasic, i.e., anterior-posterior followed by posterior-anterior (AP-PA) current direction in the coil handle, using a butterfly figure-of-eight coil (C-B60) connected to MagPro R30 stimulator with add-on Theta Burst option (MagVenture A/S, Farum, Denmark).

First, the right FDI motor hotspot was localized by moving the coil by millimeters deviation around the c3h position according to the 10–5 international EEG system (Oostenveld and Praamstra, 2001). This scalp landmark is thought to best correspond to the underlying hand representation of the motor cortex (Kim et al., 2023; Silva et al., 2021). According to the manufacturer's manual, the TMS intensity was first set at 70 % maximum stimulator output (MSO). This intensity is thought to be moderately supra-threshold, i.e., elicit EMG activity from the FDI muscle according to previous studies that measured RMT with MagPro biphasic pulses (Andrews et al., 2020). "Motor hotspot" was defined as the optimal coil position, tilt, and orientation that consistently elicited MEPs of maximum amplitudes from the relaxed FDI muscle. Despite the majority of coil orientations in our study corresponding to the conventional 45° away from the midsagittal line with the handle pointing backwards and laterally in a clockwise direction, some cases deviated more toward 0° or 90°, consistent with previous observations on biphasic pulses (Balslev et al., 2007). Following the motor hotspot localization, the coil holder (Super Flex Arm, MagVenture A/S, Farum, Denmark) was locked to fix the coil in position. In addition, we marked the coil outer shape with a felt-tipped marker on a mesh swimming cap worn by the participants. This ensured consistent coil placement throughout the session.

The first TMS measure was the resting motor threshold (RMT) using the Motor Threshold Assessment Tool (MTAT 2.1) installed on an external laptop. This app uses the parameter estimation by sequential testing (PEST) algorithm, which was endorsed by the International Federation of Clinical Neurophysiology (Rossini et al., 2015) and made freely available on http://www.clinicalresearcher.org/software.htm. At the optimal FDI hotspot, TMS intensity was decreased to 37 % MSO. The intensity was then adjusted based on the success/failure in getting an EMG response $\geq$ 50 microvolts (μV). Thirty single pulses were applied to measure the RMT as recommended (Borckardt, 2022; Koponen and Peterchev, 2022).

The second TMS measure was the MEP amplitude, operationally defined as the voltage difference between peak-to-trough (Li et al., 2022), i.e., negative to positive deflections of the MEP wave, commonly referred to as peak-to-peak amplitude (Rossini et al., 2015). In each MEP amplitude measurement, we calculated the average of 12 MEPs at 120 % RMT intensity and separated by 15 seconds. However, in a minority of cases, if the EMG signal was missed due to the subject's head movement, the coil positioning was re-adjusted and additional single pulses were applied to obtain a total of 12 automatically measurable MEP recordings by the EMG machine. Similarly, additional single pulses were applied if any of the original 12 pulses did not produce an automatically measurable MEP amplitude, potentially due to the temporal dispersion and phase cancellation phenomenon (Kimura, 2019). We measured the MEP amplitude at 5 timepoints: pre-iTBS (T_0) and post-iTBS at 4–7 (T_1), 9–12 (T_2), 17–20 (T_3), and 27–30 minutes (T_4). In each timepoint post-iTBS, the mean value of MEPs (aka, conditioned MEPs) was averaged and compared to pre-iTBS (aka, baseline MEPs) using the following equation: (conditioned MEP amplitude/baseline MEP amplitude) $\times$ 100. A value of 90–110 % represents no change, while values $<$ 90 % represent suppression, and $>$ 110 % represent facilitation of the corticospinal excitability following iTBS (Boucher et al., 2021). Grand average MEP (MEPGA) is defined as the mean value of the %change in MEP at T_1, T_2, T_3, and T_4. To evaluate unintended TMS-related sensations, participants completed the TMSens_Q questionnaire at the end of each session (Giustiniani et al., 2022).

2.3.2. Intermittent theta burst stimulation

The iTBS protocol was applied as biphasic pulses (AP-PA) using a butterfly figure-of-eight coil (C-B60) connected to a MagPro R30 stimulator with ad-on Theta Burst option (MagVenture A/S, Farum, Denmark). The stimulation protocol consisted of a 2-s TBS train of pulses repeated every 10 s for 192 s. Each TBS train comprised a 3-pulse burst 20 ms apart, i.e., 50 Hz, and repeated every 200 ms, i.e. 5 Hz, for a total of 600 pulses (Huang et al., 2005). Stimulation intensity was set at 70 % RMT for each subject (Fried et al., 2019; Goldsworthy et al., 2014).

2.3.3. Sham stimulation

The sham protocol was applied through a sham AirFilm® coil (product code: 3950–00) connected to a Magstim Super Rapid2 stimulator (Magstim, Whitland, UK). This coil was always positioned $\approx$ 30 centimeters behind the participants and run in the sham session to generate similar acoustic stimulation and clicking sounds of the active C-B60 coil, MagVenture, which was fixed over the motor hotspot at all times. In addition, all participants were asked to wear earplugs which minimized their ability to differentiate near vs. distant coils. The usage of acoustic stimulation of a second coil as sham condition has been reported previously in the literature (Barros Galvao et al., 2014; Tiksnadi et al., 2020).

2.4. Blood pressure and heart rate

Participants were asked to empty their bladder before the session and rest in the lab for 3–5 minutes without talking or moving around (Muntner et al., 2019). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured through clinically validated, semi-automated, oscillometric sphygmomanometer (Omron HEM-7120, Omron Healthcare Co., Japan) (Zhang et al., 2021). Mean arterial pressure (MAP) was calculated as MAP = DBP + 1/3(SBP – DBP) (DeMers and Wachs, 2024). Three measurements were obtained from the left upper arm while the participants sat in the TMS chair in a semi-recumbent position. These three measures were obtained before iTBS, immediately after iTBS, and at 30 minutes post-iTBS. Each measure comprised the average of two consecutive readings separated by 1 minute (Muntner et al., 2019).

2.5. Capillary blood glucose

Capillary blood samples were obtained via finger prick of the left hand to assess glucose levels using test strips and a clinically validated, portable monitor (FreeStyle Optium Neo, Abbott Laboratories, USA) (Al-Zahrani et al., 2020). Capillary blood glucose measures were obtained before iTBS, immediately after iTBS, and at 30 minutes post-iTBS.

A schematic diagram of the study protocol and experimental setup are shown in Fig. 1 and Fig. 2, respectively.

2.6. Predictors of corticospinal excitability indices

Interindividual variability of corticospinal excitability, both at the baseline (Corp et al., 2021; Pellegrini et al., 2020) and post-iTBS (Boucher et al., 2021; Corp et al., 2020; Hinder et al., 2014; Pellegrini et al., 2018a), is well-documented in the literature. Therefore, we conducted secondary analyses on the baseline data including SBP, DBP, MAP, HR, blood glucose, height, weight, and BMI to explore potential association with the TMS parameters of corticospinal excitability pre- and post-iTBS.

2.7. Data analysis

SPSS-29 software (IBM Corp., NY, USA) was used for all analyses. Graphs were generated with GraphPad Prism version 10. Data cleaning was conducted initially, including checking for normality of distribution with Kolmogorov-Smirnov test and histogram plots, conducting proper transformations, removing outliers, and replacing missing values. Cardiovascular (SBP, DBP, MAP, HR) and neurophysiological (RMT) measures were normally distributed (Kolmogorov-Smirnov ρ value > 0.05), and no outliers were detected. Blood glucose measures were non-normally distributed even after natural-log and square root transformations. However, individualizing the values to their baseline level, i.e., normalized glucose, as calculated through the equation (post-iTBS/pre-iTBS glucose $\times$ 100) as well as winsorizing one outlier, i.e., replacing it with its nearest centrally located value in the dataset (Pilowsky et al., 2024), brought all glucose values to normality. Likewise, the normalized MEP latency (nMEP latency) values were normally distributed after individualizing the dataset to the baseline values. For MEP amplitudes, both absolute and normalized values were not normally distributed. However, as followed in previous studies (Hinder et al., 2014; Perellón-Alfonso et al., 2018; Puri et al., 2016), applying natural-log transformation on the normalized MEP amplitudes Ln(nMEP amplitude) brought the dataset to normality. Due to technical issues, two MEP blocks at 30 minutes post-iTBS were missing. To account for that, the mean substitution method was followed (Gomila and Clark, 2022). As such, the average of the MEP blocks at 5, 10, and 20 minutes post-iTBS was calculated and used to replace these missing values individually. A two-way, repeated-measures, analysis of variance (2-way rmANOVA) was used to analyze Ln(nMEP amplitude) and nMEP latency separately with factors: INTERVENTION (2 levels: iTBS, sham) and TIME (5 levels: T0, T1, T2, T3, T4) as within-subject factors to examine the effect of iTBS on corticospinal excitability indices. Separate 2-way rmANOVA tests were run with factors: INTERVENTION (2 levels: active iTBS, sham iTBS) and TIME (3 levels: T0, T1, T2) as within-subject factors to examine the effect of iTBS on SBP, DBP, MAP, HR, and blood glucose. Greenhouse-Geisser correction was used when the sphericity assumption was violated as indicated by a significant Mauchly's test ($\rho < 0.05$). In case of significant F test results, rmANOVA was followed by post hoc analysis using Bonferroni adjustment. Noteworthy, the normalized baseline value was excluded from the rmANOVA analysis in previous TMS studies (Hinder et al., 2014; Puri et al., 2016; Wiratman et al., 2022) while included in others (Goldsworthy et al., 2014; Halawa et al.,

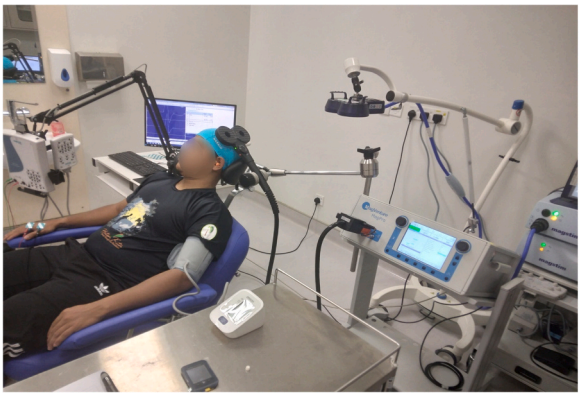

Fig. 2. Experimental setup and general procedure. Participants were seated in a comfortable motorized chair with a headrest and armrests, without visual access to the TMS or EMG equipment display. The head position was fixed through a cheek-rest attachment of the chair. Note that the sham coil was always positioned ≈ 30 centimeters behind the participants and run in the sham session to generate similar acoustic sounds of the active coil which was fixed over the motor hotspot at all times. All participants were asked to wear earplugs for hearing protection and mesh swimming caps for marking the coil's outer shape with a felt-tipped marker. Surface electromyography electrodes were attached to the right hand which was kept in a relaxed position during all measurements. Blood pressure and capillary blood glucose were taken from the left arm.

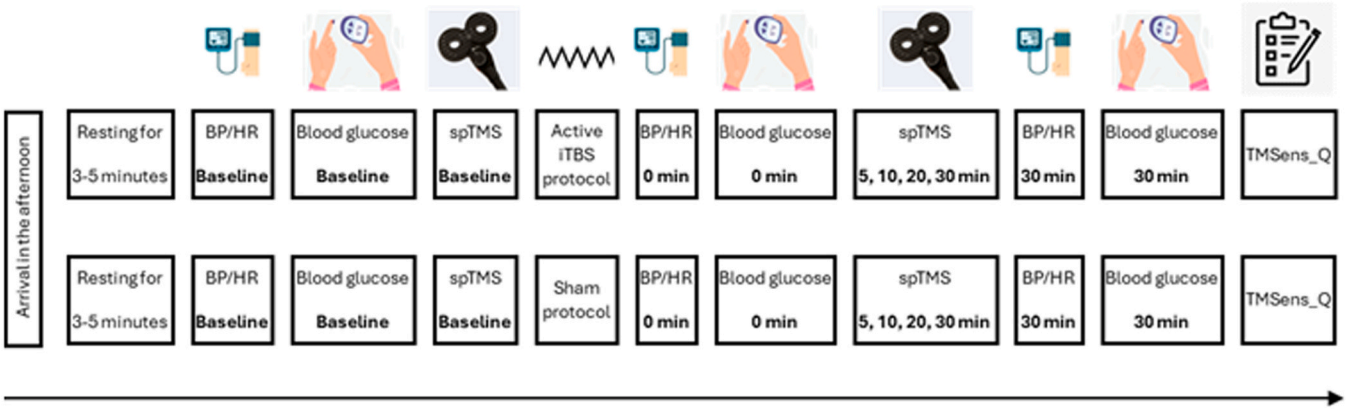

Fig. 1. Schematic representation of the experimental procedure. In each session, measures of BP/HR and blood glucose were obtained before iTBS, immediately after iTBS, and at 30 minutes post-iTBS. While measures of corticospinal excitability were obtained through spTMS before iTBS, and at 5, 10, 20, and 30 minutes post-iTBS. TMSens_Q questionnaire was filled at the end of each session. BP: Blood pressure, HR: heart rate, iTBS: intermittent theta burst stimulation, spTMS: single pulse TMS.

2021; Voytovych et al., 2012). We included the normalized baseline values in the factor TIME because we conducted post hoc Bonferroni adjustments. As such, the pairwise comparisons required that level 1 in the factor TIME remains the baseline value (pre-iTBS) in all comparisons. To explore potential predictors of the TMS parameters of corticospinal excitability, correlation analyses with baseline SBP, DBP, MAP, HR, blood glucose, height, weight, and BMI were run using Pearson's correlation coefficient (r). Significant correlations were considered potential predictors and followed by linear regression models to assess the goodness of fit. Test-retest reliability of RMT and MEP values in the 2 visits was assessed with Intraclass Correlation Coefficient (ICC) based on the absolute agreement, two-way mixed model. ICC was interpreted as having excellent reliability when ICC $\geq$ 0.90, good reliability when 0.75 $\leq$ ICC $<$ 0.90, moderate reliability when 0.50 $\leq$ ICC $<$ 0.75, and poor reliability when ICC $<$ 0.50 (Koo and Li, 2016). Normally distributed data are represented as mean $\pm$ standard deviation (Andrade, 2020), and non-normally distributed data are represented as median (interquartile range). All p values are two-tailed and considered statistically significant when $\leq$ 0.05.

3. Results

Eighteen healthy, right-handed, TMS-naïve subjects (21–33 years, 14 females) were enrolled in the study. One female subject was withdrawn during session 1 due to high RMT and coil overheating. Demographic data of the participants are shown in Table 1. The CONSORT flow diagram for participant recruitment is illustrated in Fig. 3.

3.1. TMSens_Q questionnaire

The TMS was well-tolerated in all sessions. Sleepiness was the most reported TMSens_Q sensation in 14 subjects (82.3 %) in both active and sham groups, despite asking all participants to keep their eyes open. Out of the 34 sessions, five subjects correctly identified active iTBS, and three correctly identified sham stimulation. The questionnaire results are shown in Fig. 4. All sensations were experienced during the TMS delivery and resolved at the end of each session.

3.2. Test-retest reliability of TMS measures between- and within-sessions

Across the two visits, ICC indicated excellent reliability of RMT (ICC = 0.914; 95 % CI, 0.763–0.969) and baseline MEP latency (ICC = 0.927; 95 % CI, 0.802–0.973) and good-to-excellent reliability of the baseline MEP amplitude (ICC = 0.891; 95 % CI, 0.701–0.960). Across each visit, ICC indicated an excellent reliability of MEP amplitudes at the five timepoints during both the active (ICC = 0.927; 95 % CI, 0.852–0.970) and sham sessions (ICC = 0.922; 95 % CI, 0.843–0.968). Similarly, an excellent reliability of MEP latency was observed at the five timepoints during the active (ICC = 0.991; 95 % CI, 0.981–0.996) and sham sessions (ICC = 985; 95 % CI, 968–994).

Table 1
Participant characteristics.

Variables	Mean $\pm$ SD
N	18
Age (years)	26.9 $\pm$ 3.5
Sex, F/M	14/4
Ethnicity, Malay/Chinese/Indian	13/4/1
Edinburgh laterality quotient	75.3 $\pm$ 19.3
Height (cm)	159.9 $\pm$ 8.2
Weight (kg)	58 $\pm$ 11.2
BMI (kg/m2)	22.2 $\pm$ 3.2

N = number of enrolled participants, F = female, M = male, BMI = body mass index

3.3. Effect of iTBS on corticospinal excitability in comparison to sham stimulation

On the group level, two-way rmANOVA of Ln (nMEP amplitude) did not show a significant effect of TIME, INTERVENTION, TIME $\times$ INTERVENTION, $P > 0.05$. On the subgroup level, eight participants (47 %) were responders to iTBS, i.e., their MEP grand average post-iTBS increased $>$ 110 % relative to baseline. While in the sham arm, four participants (23.53 %) were responders to the sham protocol, and their MEP grand average post-sham increased $>$ 110 % relative to baseline. Overall, three participants (17.65 %) were responders to both active iTBS and sham protocols (Fig. 5). A separate two-way rmANOVA showed a significant main effect of TIME on nMEP latency [F (4,64) = 7.708, $P < 0.001$, $\eta_p^2 = 0.325$]. However, no significant effect of INTERVENTION or TIME $\times$ INTERVENTION was evident, $P > 0.05$. Bonferroni adjusted pairwise comparisons for the main effect of TIME showed that normalized MEP latency was significantly prolonged at T_3 in comparison to T_0 (mean difference = 1.387; 95 % CI, 0.216–2.559; $P = 0.014$), and at T_4 in comparison to T_0 (mean difference = 1.787; 95 % CI, 0.628–2.947; $P = 0.001$). Absolute values and full ANOVA results of the TMS data are shown in Table 2 and Table 3, respectively.

Values are means $\pm$ standard deviation for normally distributed data and medians (interquartile range) for non-normally distributed data. RMT = resting motor threshold, MEP = motor evoked potential, MSO = maximum stimulator output, μV = microvolts, ms = milliseconds, iTBS = intermittent theta burst stimulation.

3.4. Height significantly predicted MEP latency at the baseline and normalized MEP amplitude post-iTBS

Height varied from 146 to 179 cm (159.4 $\pm$ 8.2 cm). Bivariate correlation analyses revealed that the height significantly correlated with MEP latency at T_0 in both the active iTBS ($r = 0.81$, $P < 0.001$) and sham sessions ($r = 0.83$, $P < 0.001$). In addition, there was a nearly significant negative correlation between the height and normalized MEP amplitude in the active iTBS session at T_1 (r = -0.46, $P = 0.062$) and T_2 (r = -0.46, $P = 0.065$) and a significant negative correlation at T_3 (r = -0.65, $P = 0.005$), T_4 (r = -0.66, $P = 0.004$), and MEP grand average (r = -0.68, $P = 0.003$) as shown in Fig. 6. No other correlations between TMS parameters of corticospinal excitability and baseline SBP, DBP, MAP, HR, blood glucose, weight, and BMI reached statistical significance. All data and pertinent analysis scripts can be retrieved from the Open Science Framework repository (Tomeh, 2024). Simple linear regression models in the active iTBS group showed that the subject's height significantly predicted MEP latency at T_0 [F (1,15) = 28.10, $P < 0.001$], normalized MEP amplitude at T_3 [F (1,15) = 11.03, $P = 0.005$], normalized MEP amplitude at T_4 [F (1,15) = 11.58, $P = 0.004$], and MEP grand average [F (1,15) = 13.12, $P = 0.003$].

3.5. Effect of iTBS on cardiovascular response and blood glucose in comparison to sham stimulation

Two-way rmANOVA of normalized blood glucose (nGlucose), HR, SBP, DBP, and MAP did not show a significant main effect of INTERVENTION or TIME $\times$ INTERVENTION, $P > 0.05$. However, there was a significant main effect of TIME on nGlucose [F (1.397, 22.345) = 6.179, $P = 0.013$, $\eta_p^2 = 0.279$], HR [F (2,32) = 34.480, $P < 0.001$, $\eta_p^2 = 0.683$], SBP [F (1.470, 23.526) = 12.341, $P < 0.001$, $\eta_p^2 = 0.435$], and MAP [F (1.454, 23.262) = 5.803, $P = 0.015$, $\eta_p^2 = 0.266$]. Bonferroni adjusted pairwise comparisons for the main effect of TIME showed that nGlucose was significantly higher at T_1 in comparison to T_0 (mean difference = 5.336; 95 % CI, 0.777–9.895; $P = 0.019$), HR was significantly lower at T_1 in comparison to T_0 (mean difference = 6.279; 95 % CI, 3.831–8.728; $P < 0.001$) and at T_2 in comparison to T_0 (mean difference = 6.441; 95 % CI, 3.640–9.242; $P < 0.001$), SBP was significantly lower at T_1 in comparison to T_0 (mean difference = 4.721; 95 % CI, 2.791–6.650;

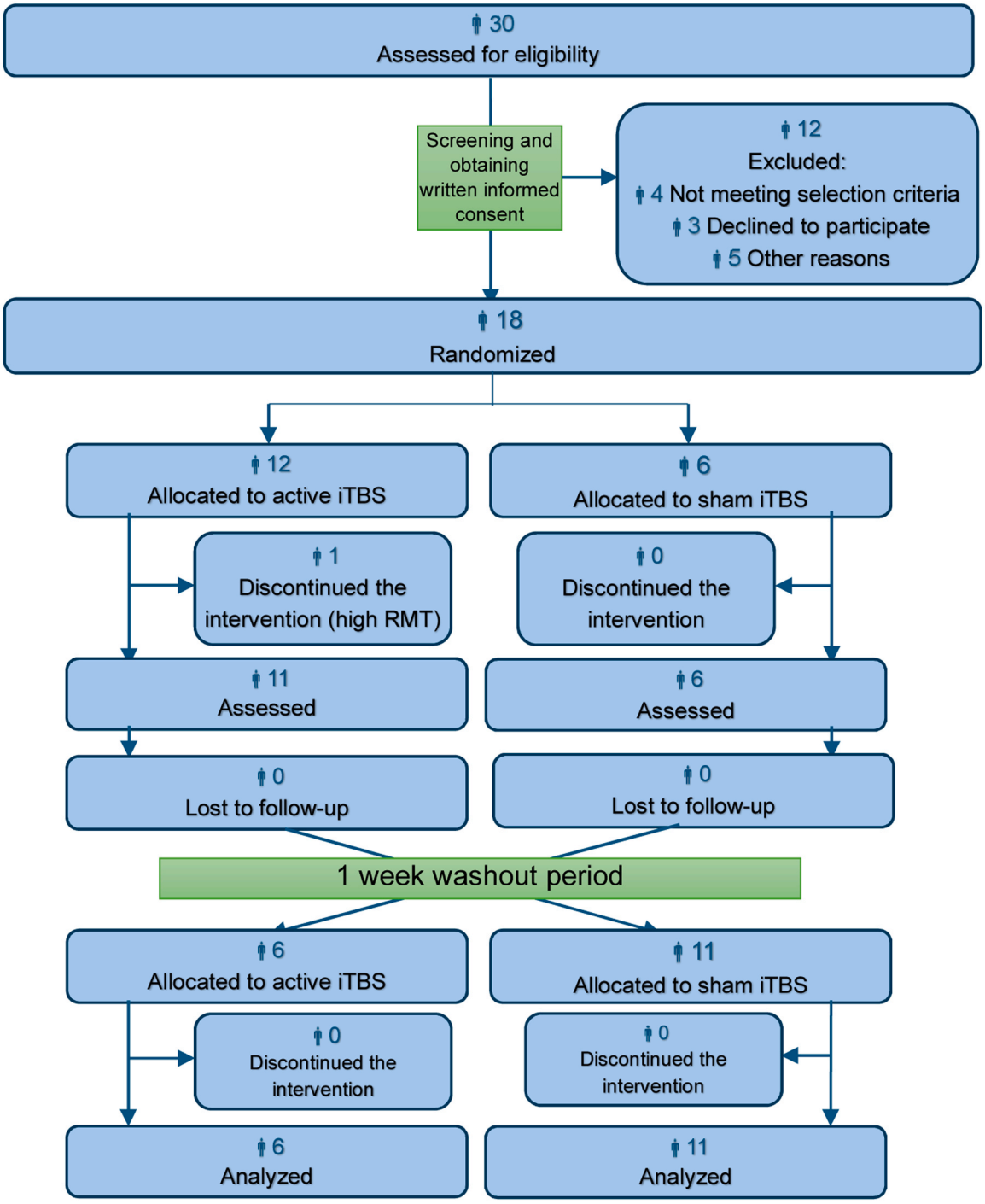

Fig. 3. CONSORT flow diagram of participant recruitment. Seventeen subjects completed the study, while one subject was withdrawn at session 1 due to high RMT and coil overheating. RMT: resting motor threshold, iTBS: intermittent theta burst stimulation.

$P < 0.001$) and in T_2 in comparison to T_0 (mean difference = 4.250; 95 % CI, 0.806–7.694; $P = 0.014$), and MAP was significantly lower at T_1 in comparison to T_0 (mean difference = 3.059; 95 % CI, 1.022–5.096; $P = 0.003$). No other pairwise comparisons reached statistical significance. Absolute values and full ANOVA results of the blood glucose and cardiovascular measures are shown in Table 4 and Table 5, respectively (Fig. 7).

Values are means ± standard deviation for normally distributed data and medians (interquartile range) for non-normally distributed data. iTBS = Intermittent theta burst stimulation, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure

4. Discussion

In the present study, we sought to explore the tolerability and efficacy of iTBS protocol on corticospinal excitability, cardiovascular response, and blood glucose in healthy young adults in comparison to sham stimulation. As the first study in a Malaysian population, the iTBS protocol was well-tolerated and none of the sessions were discontinued due to discomfort or inconvenience.

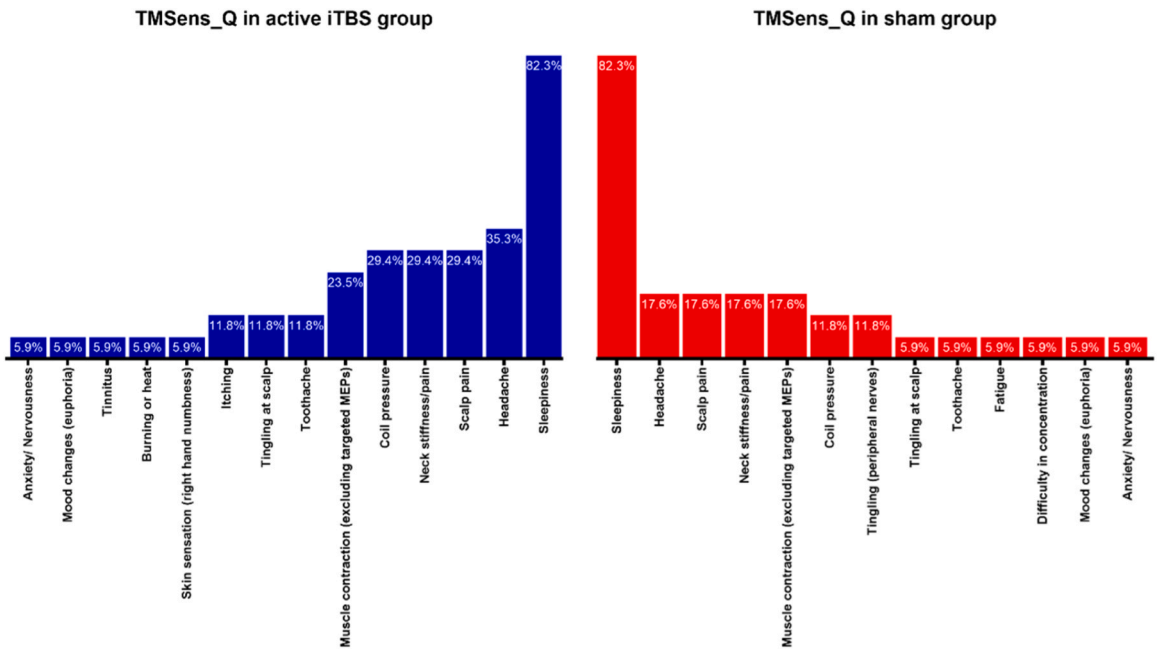

Fig. 4. Results of the standardized TMSens_Q questionnaire. The graph depicts the frequency of sensations in the active (blue bars) and sham (red bars) as demonstrated by the percentage of subjects reporting their sensations at the end of each session.

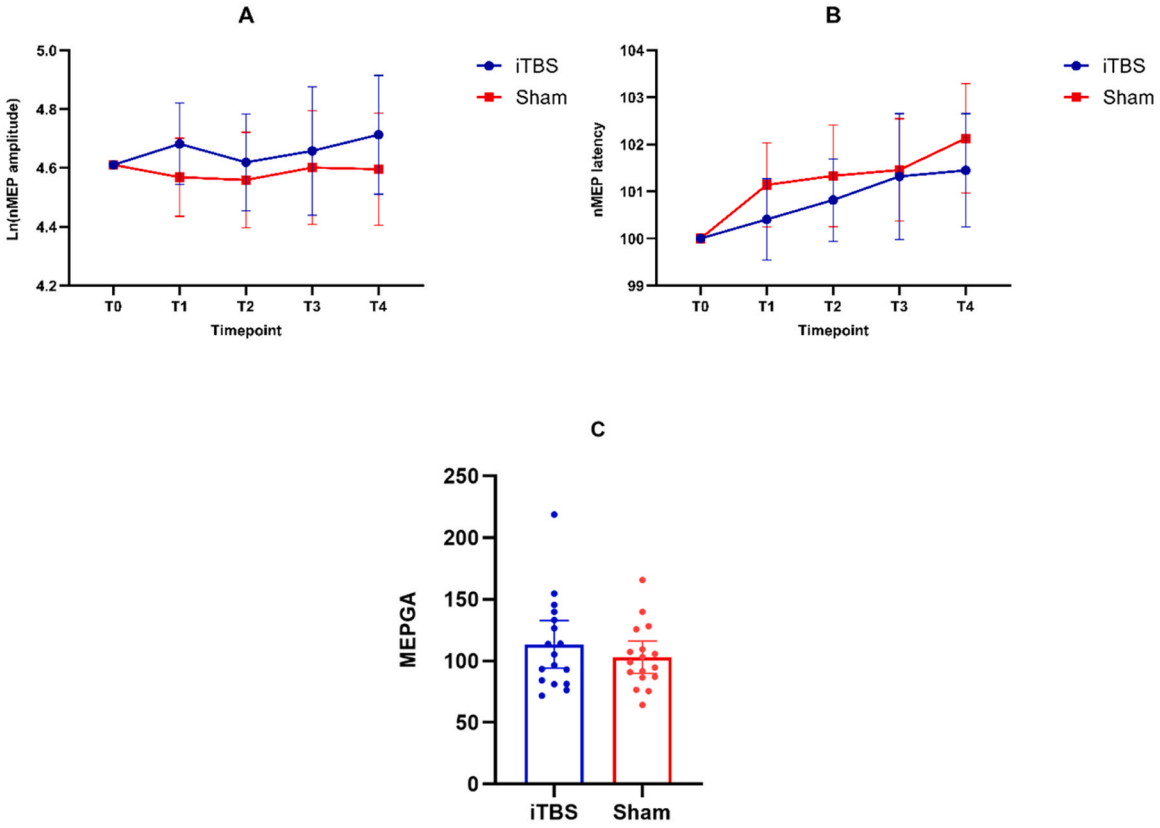

Fig. 5. Comparison of corticospinal excitability indices between iTBS and sham stimulation. (A, B) Natural log-transformed normalized MEP amplitudes (A) and normalized MEP latencies (B) plotted at every timepoint at baseline (T0) and post-intervention (T1, T2, T3, T4). (C) Grand average MEP amplitude. Error bars denote 95 % confidence interval around the mean.

4.1. Effect of M1-iTBS on corticospinal excitability and predictors of response

In contrast to the available systematic reviews and meta-analyses in the field (Chung et al., 2016; Corp et al., 2020; Wischnewski and Schutter, 2015), we did not find a significant effect of M1-iTBS on corticospinal excitability compared to sham stimulation. However, it is worth noting that the included studies were of pre-post design, rather

Table 2
Absolute values of TMS data.

Variables	Active iTBS group	Sham group
RMT — %MSO	60.53 ± 7.59	60 ± 7.52
MEP amplitude – μV		
T_0	1478 (1253.5 – 1794.5)	1433 (1054.5 – 2234)
T_1	1635 (1278.5 – 1963.5)	1403 (952.5 – 2240)
T_2	1626 (1018.5 – 2091)	1510 (1009 – 2005)
T_3	1464 (1228.5 – 1984)	1329 (1014.5 – 2475)
T_4	1680 (1107 – 2242.5)	1454 (1047.5 – 2232.5)
MEP latency – ms		
T_0	22.11 (21.37 – 22.98)	21.83 (21.34 – 22.38)
T_1	22.14 (21.37 – 23.23)	22.22 (21.48 – 22.67)
T_2	21.98 (21.35 – 23.07)	22.15 (21.58 – 22.63)
T_3	22.19 (21.34 – 23.60)	21.96 (21.54 – 22.98)
T_4	22.33 (21.65 – 23.33)	22.26 (21.93 – 22.71)

than sham-controlled studies. On the other hand, our findings are in line with recent sham-controlled studies that cast doubt on the robust effectiveness of M1-iTBS in modulating corticospinal excitability in comparison to sham stimulation (Boucher et al., 2021; Magnuson et al., 2023; Perellón-Alfonso et al., 2018).

We hereby highlight several methodological considerations in our study as every attempt was made to minimize M1 excitation and hence obtain valid results of the iTBS protocol per se. Firstly, we applied the iTBS protocol at an intensity of 70 % RMT. This is unlike most M1-iTBS studies that used an intensity of 80 % active motor threshold (AMT) (Chung et al., 2016; Corp et al., 2020), following the seminal work of Huang et al.(Huang et al., 2005). Although 70 % RMT is similar to 80 % AMT based on the "Big TMS Data" (Corp et al., 2020; Corp et al., 2021), there is evidence that persistent FDI muscle contraction during AMT measurement might affect the M1 plasticity-related measures (Gentner et al., 2008; Goldsworthy et al., 2014; Iezzi et al., 2008). Plus, RMT measurement is technically less demanding than the AMT. Hence, it requires shorter duration and less excitation to the brain (Ma et al., 2023). Secondly, we used the validated MTAT 2.1. software that applies the PEST algorithm (Rossini et al., 2015). As a result, we only applied 30 pulses in the RMT measurement as a fixed number across subjects and separated by at least 5 seconds (Borckardt, 2022; Nazarova and Asmolova, 2022). While most M1-iTBS studies thus far have used the conventional 5-out-of-10 MEP responses, which might take 50–70 pulses to estimate the motor threshold (Silbert et al., 2013). Thirdly, we used earplugs for all participants. While this had a protective effect on hearing, it also minimized the acoustic effect of TMS pulses and, consequently, the potential confounding effect of auditory evoked potentials. Recently, there has been evidence that the clicking sound of TMS coils per se might impact MEP amplitudes (Capozio et al., 2021; Nyrhinen et al., 2024; Pellegrino et al., 2022). This phenomenon might be attributed to the effect of auditory stimulation on the reticulospinal tract, which in turn modulates spinal motoneurons' excitability (Dean and Baker, 2017). Fourthly, previous sham-controlled M1-iTBS studies have applied the sham protocol through tilted coil (Perellón-Alfonso et al., 2018) or through sham coils with placed surface electrodes on the scalp to mimic the active iTBS sensations and mask the subjects to the applied protocol (Boucher et al., 2021; Magnuson et al., 2023). However, such sham protocols might stimulate the primary somatosensory cortex (S1), which in turn facilitates M1 excitability via the intracortical pathways from S1 to M1 (Ohashi et al., 2019; Park, 2022), obliterating the true difference between active iTBS and sham stimulation. However, we applied the sham protocol through the acoustic stimulation of an adjacent coil rather than applying active electrical stimulation to the scalp. Still, we did not detect a significant difference between active iTBS and sham stimulation on corticospinal excitability. Fifthly, previous M1-iTBS studies have used monophasic single pulses to probe corticospinal excitability pre- vs. post-biphasic TBS protocols. However, the literature has shown that monophasic and biphasic TMS waveform configurations stimulate different circuits inside the brain and recruit separate descending volleys in the corticospinal tract (Di Lazzaro et al., 2001; Sommer et al., 2006; Sommer et al., 2018). Therefore, we chose the same coil and biphasic waveform configuration (AP-PA) for all MEP measurements to more accurately evaluate the excitability changes in neural populations stimulated by iTBS (which applies the same AP-PA biphasic waveform). Sixthly, we collected MEP blocks with an interval of 15 seconds between the single pulses. To our knowledge, this is the longest interval among M1-iTBS studies thus far, and the least likely to produce cumulative effects between the pulses (Hassanzahraee et al., 2019; Julkunen et al., 2012; Pellicciari et al., 2016). This is corroborated by near-infrared spectroscopy studies showing that it takes ≈ 10 seconds for the brain hemodynamic changes to return to baseline after delivering suprathreshold single pulse TMS (Furubayashi et al., 2013; Mochizuki et al., 2006; Thomson et al., 2012), and transcranial doppler imaging studies showing an alteration in cerebral microcirculation after M1-iTBS (Pichiorri et al., 2012). Although we collected 12 single pulses in each MEP block to, which is below the recommended number of 20 pulses reliably estimate corticospinal excitability (Goldsworthy et al., 2016; Rossini et al., 2015), the intraclass correlation coefficient (ICC) revealed an excellent reliability of the MEP amplitudes in the sham condition. This might suggest that prolonging the inter-pulse interval to 15 seconds might reduce the number of pulses required to reliably estimate corticospinal excitability, in line with recent findings (Hassanzahraee et al., 2019). Unexpectedly, however, we found the ICC of MEP amplitudes over the five timepoints is slightly higher in the active than in the sham session. This is counterintuitive given that the iTBS protocol supposedly alters corticospinal excitability to some extent, and therefore increases the heterogeneity of MEP amplitudes and reduces their ICC. This adds another line of evidence to the lack of significant modulation of corticospinal excitability by iTBS in our study on the group level. In addition, the excellent ICC of MEP amplitudes indicates that the absence of MRI-guided neuronavigation in our setting was not a weakness of the study. This is consistent with previous sham-controlled, MRI-neuronavigated, M1-iTBS studies that similarly reported non-significant findings (Boucher et al., 2021; Magnuson et al., 2023). It also aligns with the findings of Jung et al. who reported a similar consistency of MEPs between the MRI-guided neuronavigation and the felt-tip pen hotspot methods (Jung et al., 2010). However, we acknowledge that we needed to re-adjust the coil positioning manually in a few circumstances as explained in the methodology section. Seventhly, we set the

Table 3
ANOVA results of TMS data.

Variables	TIME	INTERVENTION	TIME × INTERVENTION
Ln(nMEP amplitude)	F (4,64) = 0.245, P = 0.912, η_p^2 = 0.015	F (1,16) = 1.149, P = 0.3, η_p^2 = 0.067	F (4,64) = 0.519, P = 0.722, η_p^2 = 0.031
nMEP latency	**F (4,64) = 7.708, P < 0.001, η_p^2 = 0.325**	F (1,16) = 0.605, P = 0.448, η_p^2 = 0.036	Greenhouse–Geisser corrected F (2.412, 38.598) = 0.489, P = 0.652, η_p^2 = 0.03

Two-way repeated measures ANOVAs were performed on TMS measures, involving Ln(nMEP amplitude) and nMEP latency, using within-subject factors of INTERVENTION (2 levels: iTBS, sham) and TIME (5 levels: T0, T1, T2, T3, T4). MEP = motor evoked potential, Ln(nMEP amplitude) = natural log-transformed normalized MEP amplitude, nMEP latency = normalized MEP latency. Values in bold denote statistically significant results.

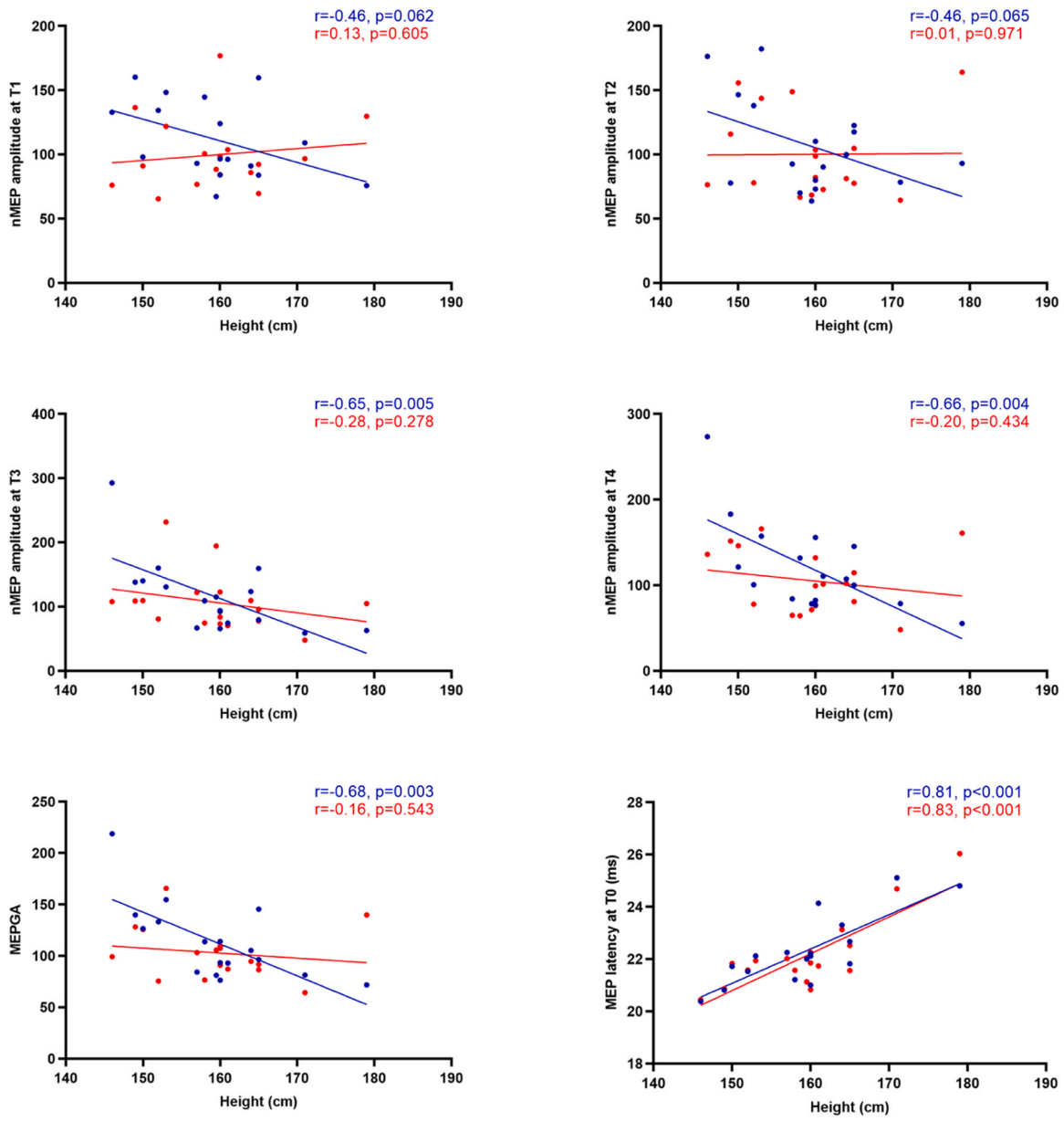

Fig. 6. Bivariate scatterplots and regression lines illustrate the association between subjects' height (x-axis) and MEP amplitudes and latencies (y-axis). The active iTBS group is shown in blue and the sham group is shown in red. Each subject is represented by two points with the same x-value due to the crossover nature of the study. All p-values are two-tailed.

band-pass filtering rate of the surface EMG machine between 1 Hz to 10 kHz and the sampling frequency at 48 kHz. At least there is some evidence that the magnitude of MEP can be affected by EMG-related settings in terms of frequency spectrum of the EMG signal and processing TMS stimulus artifacts (Groppa et al., 2012; Nikolov et al., 2021; Zschorlich et al., 2021). However, this impact has not been systematically evaluated to our knowledge.

On the subgroup level, eight participants (47 %) were responders to iTBS, i.e., their MEP grand average post-iTBS increased > 110 % relative to baseline, which is comparable to previous cluster analysis studies as reviewed by Pellegrini and colleagues (Pellegrini et al., 2018b). While in the sham arm, interestingly, four participants (23.53 %) were "responders" and their MEP grand average post-sham stimulation increased > 110 % relative to baseline. This observation might be attributed to the "noisy brain" phenomenon (Grossman et al., 2019; McIntosh et al., 2010; Protzner et al., 2010) and therefore substantiates the need to include sham protocol in iTBS studies to account for such confounding factor.

On the other hand, the active M1-iTBS protocol did not modulate MEP latencies significantly compared to sham stimulation. However, the MEP latency was prolonged considerably toward the end of the session in both active and sham groups. While MEP amplitude reflects corticospinal excitability status, MEP latency determines the conduction time taken for intracortical processing, corticofugal conduction, spinal processing, and neuromuscular transmission (Bestmann and Krakauer, 2015; Groppa et al., 2012). We attribute the MEP latency prolongation to the sleepiness reported by most subjects (82.3 %) in both the active and sham groups. This is consistent with the findings of Avesani and colleagues who reported a significant prolongation of the MEP latency during various sleep stages, involving sleepiness and non-rapid eye movement (Avesani et al., 2008), probably due to the thalamocortical hyperpolarization during sleep onset which modulates the cortical reactivity to sensory inputs (Avesani et al., 2008).

In line with previous studies (Cantone et al., 2019; Cantone et al.,

Table 4
Absolute values of blood glucose and cardiovascular measures.

Variables	Active iTBS group	Sham group
Blood glucose – mmol/L		
T_0	4.9 (4.45 – 5.55)	5.4 (4.55 – 6.40)
T_1	4.8 (4.65 – 6.00)	5.4 (4.75 – 7.40)
T_2	4.8 (4.25 – 5.40)	5.0 (4.70 – 6.15)
HR – bpm		
T_0	73.29 ± 10.60	76.94 ± 11.21
T_1	68.00 ± 7.87	69.68 ± 8.15
T_2	67.59 ± 7.53	69.76 ± 10.08
SBP – mmHg		
T_0	110.76 ± 8.73	111.20 ± 9.70
T_1	106.67 ± 8.29	105.85 ± 10.24
T_2	108.06 ± 10.15	105.41 ± 11.75
DBP – mmHg		
T_0	73.15 ± 6.83	72.00 ± 6.17
T_1	70.91 ± 6.80	69.76 ± 8.70
T_2	72.85 ± 8.28	71.15 ± 8.13
MAP – mmHg		
T_0	85.76 ± 7.00	85.06 ± 6.78
T_1	82.94 ± 6.79	81.76 ± 8.82
T_2	84.59 ± 8.54	82.59 ± 9.06

2023; Livingston et al., 2010; Livingston et al., 2013; Säisänen et al., 2008), we found a significant positive correlation between the subjects' height and MEP latencies. This is justified by the longer time it takes for the nerve impulse to transmit from M1 to the FDI muscle in taller compared to shorter subjects (Livingston et al., 2013). Surprisingly, however, we found a significant negative correlation between the subjects' height and their normalized MEP amplitudes post-iTBS. To the best of our knowledge, our study is the first to report an association between the height and neuroplasticity response to M1-iTBS. We interpret this observation in light of previous studies that reported a significant correlation between MEP latency pre-TBS and normalized MEP amplitudes post-TBS (Hamada et al., 2013; Huang and Mouraux, 2015; Volz et al., 2019). But it is worth noting that the authors in two of these studies measured MEP latencies with different coil directions and pulse waveforms to probe the late I-waves recruitment (Hamada et al., 2013; Volz et al., 2019). These waves represent high-frequency repetitive discharges of corticospinal fibers (Ziemann, 2020), and they are believed to have a significant role in the neuroplasticity induction following iTBS (Suppa et al., 2016). The third study measured MEP latency with the same coil direction and biphasic pulse waveform as the TBS protocol (Huang and Mouraux, 2015), which is similar to our setting. However, neither of these studies adjusted the MEP latency to the height of the participants, which might represent a potential confounding variable in this scenario. Taken together, we urge to further explore the role of *height* as a potential predictor for post-iTBS normalized MEP amplitudes in future studies. After all, the standard 50 Hz/5 Hz TBS protocol might not be a "one size that fits all", and the TBS frequency might need to be adjusted according to the subject's height and MEP latency, i.e., M1-to-FDI conduction time. Noteworthy, other TBS variants such as 30 Hz/5 Hz (Wu et al., 2012) and 30 Hz/6 Hz (Goldsworthy et al., 2012; Hosel and Tremblay, 2021) have also been utilized in the literature, yet to a lesser extent than the standard 50 Hz/5 Hz TBS protocol.

4.2. Effect of M1-iTBS on cardiovascular response and blood glucose

We did not find a significant effect of M1-iTBS on cardiovascular responses and blood glucose in comparison to sham stimulation. This in turn adds to the safety profile of M1-iTBS among patients with glucose and cardiovascular disorders (Oberman et al., 2011; Yozbatiran et al., 2009). However, we detected a significant effect of time on these parameters, in that SBP, MAP, and HR significantly dropped after the intervention regardless of its type, i.e., active or sham. This indicates that the reduction in cardiovascular measures was irrelevant to iTBS per se, but rather secondary to another factor, most likely the release of anxiety of a new procedure since all subjects were naïve to TMS (Foerster et al., 1997). Such anxiety response mechanism can also explain the significant increase in blood glucose after active and sham iTBS alike. However, unlike the immediate cardiovascular response, the metabolic response to anxiety and psychological stress is delayed (Russell and Lightman, 2019). This might explain the increase in blood glucose after iTBS as a delayed response to the stress hormones and anxiety at the beginning of the session. Nonetheless, it is worth noting that we did not control for the baseline glucose levels, so we did not ask the participants to fast before the session, which might represent a limitation for this outcome. In our study, however, the increase in blood glucose was noticeable at 0 min post-iTBS and returned to baseline after 30 minutes. This response pattern contrasts a previous study that reported a consistent drop in blood glucose after M1 electrical stimulation for 50 minutes post-stimulation (Kistenmacher et al., 2017). However, the blood glucose was measured in their study at 10 timepoints post-stimulation in comparison to only 2 timepoints in our study. In addition, the mechanism of action of electrical and magnetic M1 stimulation differs and is believed to involve different neural networks and molecular pathways (Rossini et al., 2015; Siebner et al., 2022).

4.3. Limitations and future directions

A number of factors confounded our study and should be

Table 5
ANOVA results of blood glucose and cardiovascular measures.

Variables	TIME	INTERVENTION	TIME × INTERVENTION
Normalized blood glucose	**Greenhouse–Geisser corrected F (1.397, 22.345) = 6.179, P = 0.013, η_p^2 = 0.279**	F (1,16) = 0.062, P = 0.807, η_p^2 = 0.004	F (2,32) = 0.235, P = 0.792, η_p^2 = 0.014
HR	**F (2,32) = 34.480, P < 0.001, η_p^2 = 0.683**	F (1,16) = 1.090, P = 0.312, η_p^2 = 0.064	F (2, 32) = 1.090, P = 0.348, η_p^2 = 0.064
SBP	**Greenhouse–Geisser corrected F (1.470, 23.526) = 12.341, P < 0.001, η_p^2 = 0.435**	F (1,16) = 0.371, P = 0.551, η_p^2 = 0.023	F (2, 32) = 2.111, P = 0.138, η_p^2 = 0.117
DBP	F (2,32) = 3.250, P = 0.052, η_p^2 = 0.169	F (1,16) = 1.207, P = 0.288, η_p^2 = 0.070	F (2, 32) = 0.102, P = 0.903, η_p^2 = 0.006
MAP	**Greenhouse–Geisser corrected F (1.454, 23.262) = 5.803, P = 0.015, η_p^2 = 0.266**	F (1,16) = 1.018, P = 0.328, η_p^2 = 0.060	F (2, 32) = 0.517, P = 0.601, η_p^2 = 0.031

Two-way repeated measures ANOVAs were performed on cardiovascular and blood glucose measures, involving SBP, DBP, MAP, HR, and normalized blood glucose, using within-subject factors of INTERVENTION (2 levels: iTBS, sham) and TIME (3 levels: T_0, T_1, T_2). HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure. Values in bold denote statistically significant results.

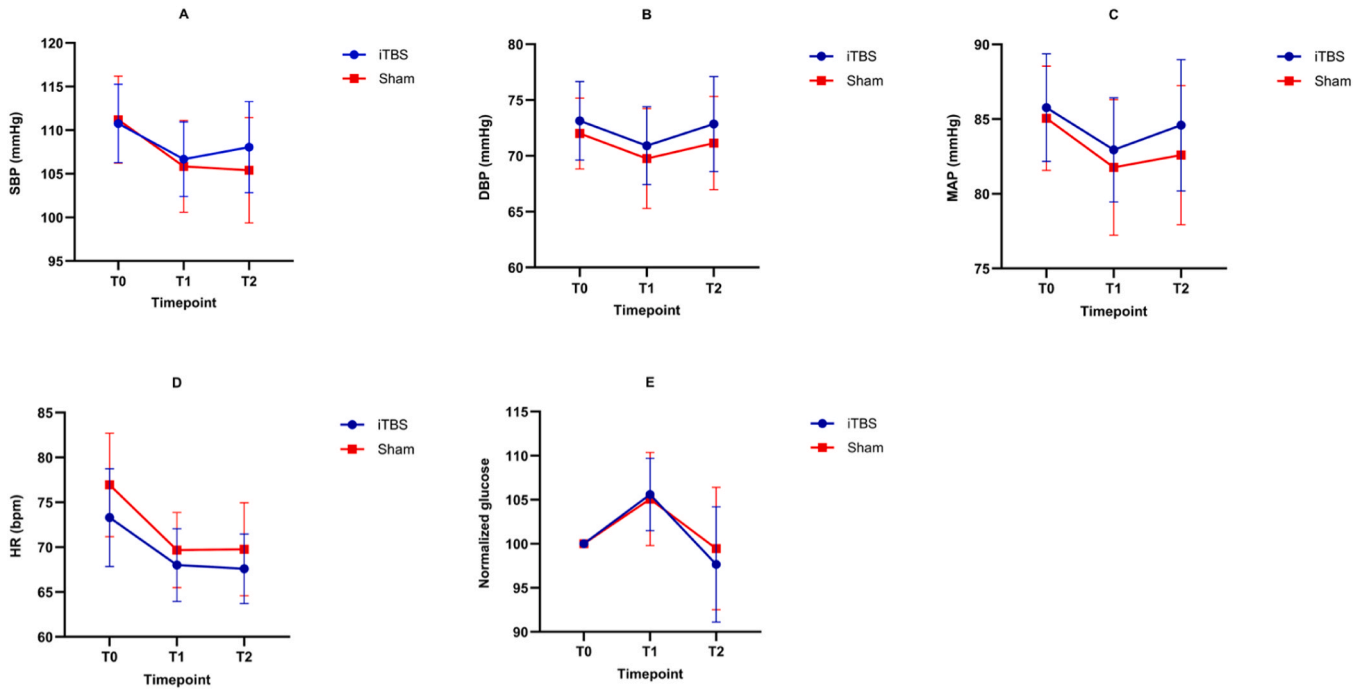

Fig. 7. Comparison of the cardiovascular and blood glucose measures between iTBS and sham stimulation. (A, B, C, D) Systolic blood pressure (A), diastolic blood pressure (B), mean arterial pressure (C), and heart rate (D) plotted at every timepoint at baseline (T_0) and post-intervention (T_1, T_2). (E) Normalized blood glucose plotted at every timepoint at baseline (T_0) and post-intervention (T_1, T_2). Error bars denote 95 % confidence interval around the mean.

acknowledged. Firstly, despite asking all participants to keep their eyes open, most reported sleepiness during the sessions (28/34 sessions). Therefore, the fluctuation in arousal state and consequently cortical excitability could have impacted our MEP amplitudes and latencies (Avesani et al., 2008; Conte et al., 2007; Kamke et al., 2012). Secondly, a recent study found that the most significant alteration of corticospinal excitability was evident immediately after the intervention, i.e., at 0-minute post-iTBS (Seybert et al., 2023). However, our study measured the first MEP at a 5-minute timepoint post-iTBS. Thirdly, our measures of the cardiovascular and blood glucose changes were only obtained at two timepoints post-iTBS (Al et al., 2023; Paci et al., 2024). Thirdly, the population involved in the final analysis showed a female predominance with 76.5 % females and 23.5 % males.

Given this, we recommend future M1-iTBS studies to be conducted in a sham-controlled, crossover design, minimize cortical excitation and unnecessary TMS pulses to obtain valid results of the iTBS protocol per se, control for the level of attention and arousal state, explore the role of subjects' height and gender on responder status, and monitor blood glucose and cardiovascular responses continuously or more frequently than our study. In addition, we recommend measuring the MEP amplitudes and latencies with the same pulse waveform, coil type, and coil orientation as the TBS protocol to more accurately assess the excitability status of the neural populations stimulated by TBS.

5. Conclusions

In the present study, we did not find significant effects of M1-iTBS on corticospinal excitability, blood glucose, and cardiovascular response at the group level compared to sham stimulation. There was a subgroup of participants (47 %) who were considered responders to iTBS, i.e., their MEP grand average post-iTBS increased to $>$ 110 % compared to baseline. At the same time, however, there was a subgroup of participants (23.53 %) who also "responded" to the sham protocol, and their MEP grand average post-sham increased to $>$ 110 % compared to baseline. Overall, three participants (17.65 %) responded to both active iTBS and sham protocols. Surprisingly, however, we found a significant negative correlation between the subjects' height and their normalized MEP amplitudes post-iTBS only, but not sham. We thereby urge future studies to delve deeper into the influence of height on M1 plasticity induction, prospectively and retrospectively, and utilize the TMSens_Q to explore the subjects' arousal state and its potential confounding effect on corticospinal excitability.

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CRediT authorship contribution statement

Basri Hamidon: Writing – review & editing, Resources, Project administration, Funding acquisition. **Inche Mat Liyana Najwa:** Writing – review & editing, Validation, Project administration, Funding acquisition. **Wan Sulaiman Wan Aliaa:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Ling King-Hwa:** Writing – review & editing, Validation, Project administration, Funding acquisition. **Abu Zaid Zalina:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Yusof Khan Abdul Hanif Khan:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Tomeh Abdulhameed:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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.

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Data Availability

Deidentified raw datasets of this study are freely available on the Open Science Framework repository at https://doi.org/10.17605/OSF.IO/VRNC4

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