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The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke: Study Protocol for a Randomized Controlled Trial

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Abstract

Introduction: Intermittent Theta Burst Stimulation (iTBS), a form of repetitive Transcranial Magnetic Stimulation (rTMS), delivered to the ipsilesional primary motor cortex (M1), appears to enhance the brain's response to rehabilitative training in patients with stroke. However, its clinical utility is highly subject to variability in different protocols. New evidence has reported that, preceding iTBS, with continuous theta burst stimulation (cTBS) may stabilize and even boost the facilitatory effect of iTBS on the stimulated M1, via metaplasticity. The aim of this study is to investigate the effects of iTBS primed with cTBS (i.e., priming iTBS), in addition to robot-assisted training (RAT), on the improvement of the hemiparetic upper limb functions of stroke patients, and to explore potential sensorimotor neuroplasticity using electroencephalography (EEG).

Methods and analysis: A three-arm randomized controlled trial (RCT) will be performed, with an estimated total of 36 patients with chronic stroke. All participants will be randomly allocated to receive 10 sessions of rTMS with different TBS protocols (cTBS+iTBS, sham cTBS+iTBS, and sham cTBS+sham iTBS), three to five sessions per week, for two to three weeks. All participants will receive 60 minutes of RAT after each stimulation session. Primary outcomes will be assessed using Fugl-Meyer Assessment – Upper Extremity scores and Action Research Arm Test. Secondary outcomes will be assessed using kinematic outcomes generated during RAT, and EEG.

Ethics and dissemination: Ethical approval has been obtained from The Human Subjects Ethics Sub-committee, University Research Committee of The Hong Kong Polytechnic University (Reference number: HSEARS20190718003). The results yielded from this study will be presented at international conferences and sent to a peer-review journal to be considered for publication.

(268 words)

Trial registration number: NCT04034069.

Keywords: Theta burst stimulation; stroke; hemiparetic upper limb; priming; metaplasticity.

Article Summary

- Strengths and limitations of this study

- The present study is the first randomized controlled trial to explore the effects of priming iTBS in regard to facilitating hemiparetic upper limb recovery in patients with stroke.
- This study investigates sensorimotor plasticity, along with the improvement of upper limb functions, in association with priming iTBS.
- The study attempts to potentiate the response to iTBS via an inhibitory priming session and thereby improve its clinical utility in stroke rehabilitation.
- The results of this study will contribute to the optimal use of TBS in poststroke upper limb rehabilitation.
- The present study restricts the experimental sample to chronic stroke patients residing in community-dwellings. Future studies with larger stroke cohorts or at the acute phase should be conducted.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been extensively investigated as an add-on form of therapy for stroke rehabilitation.[1] rTMS is usually limited to frequencies of 20 Hz or less, due to safety concerns, in human studies.[2] However, in animal studies, effects on synaptic plasticity are usually induced by repeated short bursts of high-frequency (> 50 Hz) stimulation, given at a frequency from 3 to 5 Hz and known as theta burst stimulation (TBS).[3] Huang *et al*. were the first to investigate the neurophysiological effects of TBS, delivered via a magnetic stimulator, in the human primary motor cortex (M1), and demonstrated that 600-pulse intermittent theta burst stimulation (iTBS) enhanced corticomotor excitability in healthy human subjects, whereas 600-pulse continuous theta burst stimulation (cTBS) did the opposite.[4] Serial TBS sessions delivered at a relatively low intensity were subsequently investigated in stroke survivors and safety concerns regarding TBS in this population appear to be minor and rare.[5-8] Various experiments with humans have also demonstrated that TBS is able to induce neuroplastic changes of the stimulated M1 in a relatively short conditioning period (i.e., 40 seconds for standard 600-pulse cTBS and three minutes for standard 600-pulse iTBS),[9] thus reducing the time spent receiving treatment.

A substantial number of clinical trials with stroke patients have revealed that iTBS of

the ipsilesional M1 significantly improves hemiplegic arm[5 8 10-12] and hand[6] motor functions, compared to sham stimulations. Similar effects have also been observed in studies using cTBS of the contralesional M1.[13 14] However, some trials have not shown any additional benefits on upper limb motor outcomes from iTBS or cTBS in stroke survivors, in contrast to sham TBS.[7 15] A recent meta-analysis showed that a pooled standardized effect size of iTBS was 0.60, while that of cTBS was 0.35 for upper limb motor outcomes in patients with stroke,[16] indicating that the increment of the excitability of the affected M1 through iTBS is critical for improving the brain's response to motor training in patients with stroke. However, substantial response variability regarding iTBS among humans may contribute to the use of different protocols among current studies,[17 18] which limits their clinical utility.

It has been shown that the history of neuronal activities is one of the major factors that could influence the brain's response to TBS.[19] Synaptic plasticity is regulated by previous neuronal activities via metaplasticity. Metaplasticity is a neuroprotective mechanism that modulates the threshold of synaptic plasticity to ensure that the neural system cannot be predominated by long-term potentiation (LTP) or long-term depression (LTD).[20] Excitatory rTMS over the M1 may be unable to facilitate corticomotor excitability when the neuronal activities have already been elevated

before stimulation, which is likely happening when patients with stroke receive extensive training before non-invasive brain stimulation.

Considering the mechanism of metaplasticity, several priming stimulation protocols, designed to incorporate a priming session followed by a stimulation session, have been investigated with healthy individuals.[21] An inhibitory priming stimulation via cTBS may ensure or even boost the facilitatory effect of subsequent excitatory stimulation sessions via iTBS. In healthy individuals, this priming protocol seems to amplify the facilitatory effect of excitatory stimulation, compared with iTBS alone, as reflected by the increased amplitude of motor evoked potential (MEP).[22-24] To the best of our knowledge, no study has investigated the effects of priming iTBS protocols in patients with stroke to date.

Various neurological biomarkers of stroke motor recovery have been proposed.[25] Electroencephalography (EEG), a non-invasive measure of cortical neuronal oscillation, is of great interest, because it is a relatively convenient and well-tolerated brain imaging technique for patients with stroke. Sensorimotor event-related desynchronization (ERD), a neurophysiological marker of sensorimotor activation, could be induced through either action observation or action execution.[26] Previously, attention has been

paid to movement-related sensorimotor ERD, which has been shown to be correlated with the severity of hemiplegia in patients with stroke.[27 28] Subsequently, researchers began to investigate sensorimotor ERD induced by observing mirror visual feedback (MVF) in healthy adults and patients with stroke.[29 30] A pilot study has demonstrated that multiple sessions of iTBS appear to enhance MVF-induced sensorimotor ERD in healthy adults.[31] So far, MVF-induced sensorimotor ERD has not been used as an outcome of neuroplasticity in any clinical stroke trial in order to examine its potential as a biomarker for stroke motor recovery.

Therefore, our study has two objectives: First, we investigate the effects of 10 sessions of rTMS using different TBS protocols (i.e., cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS plus sham iTBS), in addition to standard robot-assisted training (RAT) for both the proximal and distal joints of the hemiparetic upper limb, delivered across three to five sessions per week for two to three weeks, on improving the hemiparetic upper limb functions of stroke survivors. Fugl-Meyer Assessment - Upper Extremity (FMA-UE) scores and Action Research Arm Test (ARAT) will be used as the primary outcome measures. Safety profiles will be systematically collected during each session of the intervention, using a standard questionnaire. Second, we investigate the effects of different TBS protocols, cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS

plus sham iTBS, in addition to RAT, on upper limb kinematic outcomes yielded from each RAT session, and sensorimotor ERD induced by hemiparetic hand movement and observation of the MVF of nonparetic hand movement, in patients with stroke.

Methods

This study protocol has been written according to the Standard Protocol Items for Randomized Trials statement.[32]

Study design

This study is designed as a three-arm, parallel group, sham-controlled RCT. Potential participants with stroke will be recruited through convenience sampling from self-support groups in the community in Hong Kong. The study will be conducted in a local university laboratory.

Inclusion and exclusion criteria

Participants must meet all of the following criteria: (1) have a diagnosis of a unilateral ischemic or hemorrhagic first-ever stroke; (2) with stroke onset of one year to six years before the study; (3) between 18 and 75 years old; (4) reside in community dwellings; (4) with residual upper limb impairment $\geqslant$ second level in the Functional Test for the

Hemiplegic Upper Extremity (FTHUE).[33] FTHUE levels two to four are defined as low upper limb functioning poststroke, and levels five and seven are defined as high upper limb functioning poststroke; (5) able to understand simple verbal instruction and follow one-step commands; and (6) able to give informed written consent to participate in the study.

Although TBS is often regarded as safe for certain subjects, the greatest acute risk of TMS is the rare occurrence of induced seizures. Besides seizures, other risks include minor pain, such as a headache or local discomfort, minor cognitive changes, and psychiatric symptoms. In this study, patients who meet any of the following rTMS contraindications will not be included: (1) unstable medical condition; (2) history of epileptic seizures, unconsciousness, or intracranial hypertension; (3) serious heart disease; (4) pregnant; (5) significant aphasia or difficulty understanding the instructions given by the investigators; (6) with metal implants *in vivo*, such as a pacemaker, artificial cochlear, or implant brain stimulator; (7) history of receiving a craniotomy; or (8) does not consent to TBS intervention.[2] To ensure safety, the participants will be under the supervision of at least one investigator who has completed training in TMS. All participants will undergo a safety screening for the potential risks of TMS to ensure they are eligible to participate in this study.

In addition to TMS contraindications, participants who meet any of the following criteria will be also excluded: (1) previous diagnosis of any neurological disease excluding stroke; (2) presence of any sign of cognitive problems (Abbreviated Mental Test, Hong Kong Cantonese version < 6/10);[34] (3) patients with extreme spasticity over the elbow or wrist in the hemiparetic upper limb (Modified Ashworth score > 2),[35] or severe pain that hinders upper limb movement; (4) other notable impairments of the upper limb not affected by stroke (e.g., a recent fracture, severe osteoarthritis, congenital upper limb deformity); and (5) concurrent participation in upper limb rehabilitation training in a hospital, university laboratory or other rehabilitation settings, or active participation in another clinical trial.

Sample size estimation

Since the difference among the effects of priming iTBS in hemiparetic upper limb training has not been previously investigated, we have estimated the sample size based on current studies comparing iTBS and sham stimulation. A recent meta-analysis yields a pooled Cohen's d of 0.60 for a two-group design in favor of iTBS improving upper limb motor outcomes, in contrast to sham stimulation.[16] An effect size (d) of 0.60 corresponds approximately to an effect size (f) of 0.30 for a study design of three-group

comparisons. An estimate of sample size for each group in a three-group design, given a power of 0.80 and a two-tailed alpha error probability of 0.05, is 27 patients in total. When considering the drop-out rate of 20%, we therefore plan to recruit 12 participants for each group (a total of 36) for this study.

Randomization

Three parallel groups will be employed: (1) cTBS plus iTBS; (2) sham cTBS plus iTBS; and (3) sham cTBS plus sham iTBS. The collection of demographic characteristics (age, gender, education, side of hemiplegia, handedness, type of stroke, time from onset to treatment, lesion site(s)) and baseline assessments will be performed prior to randomization. Participants' medical information related to their stroke will be retrieved from the electronic clinical management system in the hospital after receiving consent. All participants will be randomly allocated in a 1:1:1 ratio to each group after the screening and baseline assessments have been carried out. A random sequence will be generated using Minimize software.[36] Participants will be pre-stratified based on their hemiparetic upper limb functioning (i.e., FTHUE high functioning *vs.* low functioning). The allocation sequence will be concealed from all investigators and assessors.

Intervention

TBS session

A total of 10 sessions of TBS will be delivered using MagPro magnetic stimulators (MagVenture, Denmark) connected with a figure-of-eight coil. Resting motor threshold (RMT) is defined as the minimum stimulation intensity over the hot spot that could elicit a motor evoked potential (MEP) of no less than 50 μv in three out of six trials over the contralesional first dorsal interosseous (FDI). The stimulation point is the hotspot mirrored over the midsagittal line (i.e., ipsilesional M1), verified and maintained by a TMS-navigation system (Localite, Bonn, Germany).

We follow the standard 600-pulse TBS protocol proposed by Huang *et al.*[4]: iTBS: 20 trains of 10 bursts given with eight-second intervals, with a total of 600 pulses, around 3-minute per session; cTBS: 20 trains of 10 bursts given with 0.2-second intervals, with a total of 600 pulses, around 40 seconds per session. All stimulations will be delivered over the ipsilesional M1. The intensity of the TBS will be set at 70% RMT. Sham cTBS will be delivered with the same coil, but the intensity will be reduced to 20% of the individual RMT. The interval between the priming session and the conditioning session will be 10 minutes.[22 37] All participants will be informed that TBS is delivered in a subthreshold intensity that cannot induce significant limb movement or somatosensory

perception.

Robot-assisted training

Participants will be required to undergo two forms of RAT for the proximal and distal joints of the hemiparetic upper limb, respectively, after each TBS session. RAT will commence five minutes after the completion of the TBS session.[11] A Fourier M2 robot (Fourier Intelligence Co. Ltd., Shanghai, China) will be used for the upper limb proximal joint training. The Fourier M2 robot is an end-effector robot-assisted upper limb rehabilitation device, supported by tailored interactive television games in the device. A HandyRehab hand robot (Zunosaki Company Limited., Hong Kong SAR, China) will be used for upper limb distal joint training. The device provides power-driven extension and grasping force to the fingers and thumb in order to assist the patient with opening and closing the paretic hand by means of surface electromyography (EMG) triggered from the signals through the forearm extensors and flexors. Active and passive modes are available in both robots. Whenever patients are unable to use the active modes due to the severity of the upper limb hemiplegia, passive modes will be used.

Proximal joint training

The Fourier M2 robot targets (1) flexion and extension of the shoulder joint; (2) flexion and extension of the elbow; (3) internal and external rotation of the shoulder joint; and (4) abduction and adduction of the shoulder joint. Before each training session, the size of the maximal active range of motion (ROM) for the hemiplegic upper limb will be assessed for each participant. Two-minute warm-up sessions will be delivered before and after each training session, in which participants will receive passive-mode RAT to mobilize the paretic upper limb. The movement trajectory will be predefined as a square and its size will be calculated based on participants' maximal active ROM. In the training session, the participants will be asked to move their hemiparetic upper limb to reach sequentially presented targets in an interactive game. Each proximal joint training session will last for around 30 minutes, with a break of five to 10 minutes (see Figure 1A for a demonstration of proximal joint RAT). The assistive mode will be used to train the patients with limited voluntary shoulder and elbow movement (i.e., the patient initiates the movement and the robot then produces assistive force according to the subject's effort). For patients who cannot initiate movement by themselves, the passive mode will be used. The active mode and resistive mode will be used to train the patients with voluntary shoulder and elbow movement. Each participant has to sit in front of the robot with a computer screen attached to the device. The participant will wear a trunk-fixed belt to minimize compensatory movement of the trunk during training.

Distal joint training

The HandyRehab hand robot is lightweight, powered by lithium batteries, and allows the subject to perform a full hand grasp/release movement in either the spherical grip or cylindrical grip mode. The EMG trigger threshold will be adjusted based on patients' hemiplegic arm function. Participants will be instructed to perform the different types of hand movements to pick up an object (i.e., a ball, sponge, or a cup) on a table, move it vertically and/or horizontally to four predefined targets, and release the object. The distance between the targets and participants will be adjusted based on their active ROM of proximal joints in the paretic upper limb. The EMG-triggered level will be adjusted based on patients' ability (i.e., active mode) and gradually increased as the training progresses. For patients without any detectable EMG signal from the paretic forearm, the passive mode will be used. Each distal joint training session will last for around 30 minutes, with a break of five to 10 minutes (see Figure 1B for a demonstration of distal joint RAT). In total, each RAT session lasts for approximately 60 minutes (30 minutes for proximal joints and 30 minutes for distal joints), with 10 sessions in total. An investigator with a background in occupational therapy will supervise each participant during each robot training session to ensure the correct positioning is used and that and participants become familiar with the training.

Outcome measurements

Primary outcomes

The FMA-UE and ARAT will be used as the primary outcomes for this study.[38] The FMA-UE is a clinical assessment for upper limb motor impairment after stroke. It includes 33 items assessing the movement, coordination, and reflex actions of the shoulder, elbow, forearm, and wrist, and the hand joints of the paretic arm. Each item consists of a three-point scale (zero, one, and two), with a total maximum score of 66. The minimal clinically important difference (MCID) of the FMA-UE is 5.25 points.[39] The FMA-UE will be conducted at four time points: baseline, mid-term (i.e., after five sessions), post-training (i.e., after 10 sessions), and follow-up (i.e., two weeks after the completion of all training sessions). An assessor who is unaware of the treatment allocation will carry out the assessment for each participant.

The ARAT is a clinical assessment for upper limb functional activities for patients with stroke. The ARAT assesses proximal and distal components of upper limb function. It consists of four subscales: grasp, grip, pinch, and gross movement. It has 19 movement tasks, each graded using a four-point scale (total scores range from 0 to 57). The MCID of ARAT is 5.70 points.[40] ARAT will be conducted at the same four time points as the

FMA-UE. An assessor who is unaware of the treatment allocation will carry out the assessment for each participant. Assessors will be trained and tested by the principle investigator, before conducting clinical assessments. Upon the follow-up assessment, participants will be paid 100 Hong Kong dollars as the travel allowance.

Secondary outcomes

Kinematic metrics generated during each session of RAT will be used as secondary outcomes for the participants' upper limb function. The following kinematic metrics retrieved from the M2 robot will be used as the upper limb motor outcomes in a further analysis: (1) the size of the maximal active ROM; (2) the mean velocity of movement during the training session; and (3) the movement trajectory during the training session. Movement trajectory will be further calculated as the hand-path ratio, which is defined as the real distance divided by the shortest distance between object targets.[41]

In order to investigate the potential neuroplasticity elicited by the training, we will invite patients to participate in EEG examinations. We expect that around five patients from each group will voluntarily take part in the EEG examinations before and after the intervention. For participants who participate the EEG part, 400 Hong Kong dollars will be paid as an incentive. Kinematic and EEG outcomes will be assessed in a non-

blinded manner (see Figure 2 for a flowchart).

EEG acquisition

EEG will be captured with a 64-channel cap using a Digital DC EEG Amplifier. Electrode impedance will be kept below 10 kOhm and the signal will be sampled at 1000 Hz. Movement-related ERD and MVF-induced ERD will be evaluated in this study. For movement-related ERD, participants will be asked to perform finger taps three times (or attempt to move their finger if they cannot perform the movement fluently) on a computer keyboard with the index finger of their unaffected side, in response to auditory cues (i.e., a 300-ms beep sound) delivered at random intervals (from seven seconds to 10 seconds), and to relax their hand after the completion of the movement.

For MVF-induced ERD, participants will be asked to perform finger taps three times on a computer keyboard with the index finger of their unaffected side, in response to auditory cues delivered at random intervals (from seven seconds to 10 seconds),[42] and to relax their hand after the completion of the movement. A widely used EEG paradigm exploring the effects of MVF will be utilized in the present study;[29 30 42-44] movements will be performed under two conditions. (1) MVF of the hand movement: Participants

will be required to perform unilateral finger tapping while viewing MVF. MVF will be created using a physical mirror (406 × 432 mm) placed over their midsagittal plane, between both arms. (2) Direct visual feedback (DVF) of the hand movement: Participants will be required to perform unilateral finger tapping while directly looking at their moving finger. The affected hand will be hidden by a non-reflective board.

The order of conditions will be allocated randomly by drawing lots. A total of 60 movements will be collected for each condition (affected index movement, unaffected index with mirror view, and unaffected index with direct view), with 180 movements in total.

EEG preprocessing

Raw EEG signals will be band-pass filtered between 1 and 80 Hz and then down-sampled at 250 Hz. Additionally, a 50-Hz notch filter will be applied. Data will be offline re-referenced to bilateral mastoid electrodes. Signals with significant movement artifacts and long-term eye closure will be rejected during a visual inspection. Subsequently, EEG will be segmented in 7000 ms epochs (pre-stimulus -3000 ms and post-stimulus 4000 ms, with 0 as the first finger tap). Eye movement artifacts will be corrected using an independent component analysis algorithm.[45] Typical components

reflecting the eye blinks and horizontal movements will then be rejected.

EEG time-frequency analysis

Clean epochs will be analyzed in a time-frequency domain. The event-related spectral perturbation (ERSP) method using the *newtimef* function of EEGLAB[46] will be used to compute the ERD power. The ERD power will be baseline corrected. Subsequently, the power will be averaged across all trials and converted to log power. Averaged ERD powers at electrode sites C3 (ipsilesional hemisphere, IH) and C4 (contralesional hemisphere, CH) will be extracted. Data from patients with right brain lesions will be flipped to ensure that C3 channels stand for IHs and C4 channels stand for CHs.

For movement-related ERD, the power at C3 will be used for further analysis. For MVF-induced ERD, the powers at IH and CH during the movement phase will be extracted and an asymmetric index will be calculated with the following formula:[47]

$$\text{Asymmetric index} = (\text{IH ERD power}) - (\text{CH ERD power})$$

The difference of asymmetric indices under the mirror view and direct view will be used to evaluate MVF-induced sensorimotor ERD[42 43] and used in a further analysis.

A more negative value indicates more activation toward the ipsilesional sensorimotor area, during the mirror view condition, compared to the direct view condition. Mu-1 (8-10 Hz), mu-2 (10-12 Hz), beta-1 (12-16 Hz), and beta-2 (16-30 Hz) will be investigated separately.

Safety profile investigation

A side-effects survey will be distributed upon completion of each TBS session. See Figure 3 for an overview of the proposed trial.

Statistical Analysis

Statistical analysis will be performed using SPSS version 23.0. A mixed-effects model with random intercepts and slopes will be used to detect any significant differences in the rate of change in motor outcomes and sensorimotor ERD between the three groups, because of its superiority in analyzing repeated measures data and dataset with missing values. Group effects, time effects, and group-by-time interaction effects will be included as fixed effects, and the random intercept and random slope of change in the dependent variables over time will be included as random effects. Between-group

differences will be investigated using the interaction effects. Maximum likelihood estimation will be chosen as the estimation method. The covariance structure is assumed to be unstructured. For post-hoc comparisons, the level of significance will be set at $p < 0.017$ after Bonferroni adjustment (0.05/3; n = number of comparisons), for the comparison of interaction effects. Cohen's d will be calculated to determine the effect size of the change scores for the behavioral motor outcomes between groups. Immediate training effects (data from baseline to post-training) and the durability of training effects (data from post-training to follow-up) will be separately investigated with mixed-effect models. Frequency scores for each reported side effect and the percentage of participants who pass the MCID of the FMA-UE and ARAT will be compared using Chi-squared tests between the three groups.

Patient and public involvement

Patients will be invited to participate in this study via advertisements. Several self-help stroke organizations will be notified in order to promote the enrollment. Patients will not be involved in participant recruitment. The results of the evaluation can be released to participants upon request.

Ethics and dissemination

This randomized controlled trial was registered on 24 July 2019 (https://clinicaltrials.gov, see supplementary section for trial registration data). The study has launched on 9th September 2019 and will continue for around a year. The study will be conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent forms will be collected from each participant before the study begins (see a template of written consent form in supplementary section). Ethical consideration has been sought from the human subject ethics subcommittee of the Hong Kong Polytechnic University. Any modifications to this study protocol will also be reviewed by the subcommittee. This study will only include participants who have given informed written consent and the confidentiality is assured. All original data will be kept in strictly private. During the study, written data will be stored in a safe place; after the study, all data will be input to a computer by the principle investigator and a backup of the data will be kept on a hard drive, which will be stored in a safe place. The input data will be double checked by another research assistant. Personal data will be discarded after three years. Due to the small expected sample size of this proof-of-concept study, a data monitoring committee was not deemed to be required. We will not perform interim analyses until the completion of this study. The results of this study will be presented at international conferences and sent to a peer-reviewed journal to be considered for publication.

(4108 words)

Authors' contributions: JZ and KF were involved in the conception and design of the research. JZ wrote up the first draft of the research. KF reviewed and edited the manuscript. JZ and KF approved the submission of the final version of the manuscript.

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Figure Legends

Figure 1. A demonstration of RAT.

*Note: The persons depicted are not patient and were taken with the participants knowledge.

Figure 2. Flowchart of the proposed randomized controlled trial.

Figure 3. Schedule of participant recruitment, assessments, and intervention. Abbreviation: iTBS: intermittent theta burst stimulation; RAT: robot-assisted training; FMA-UE: Fugl-Meyer Assessment-Upper Extremity scores; ARAT: action research arm test; EEG: electroencephalography.

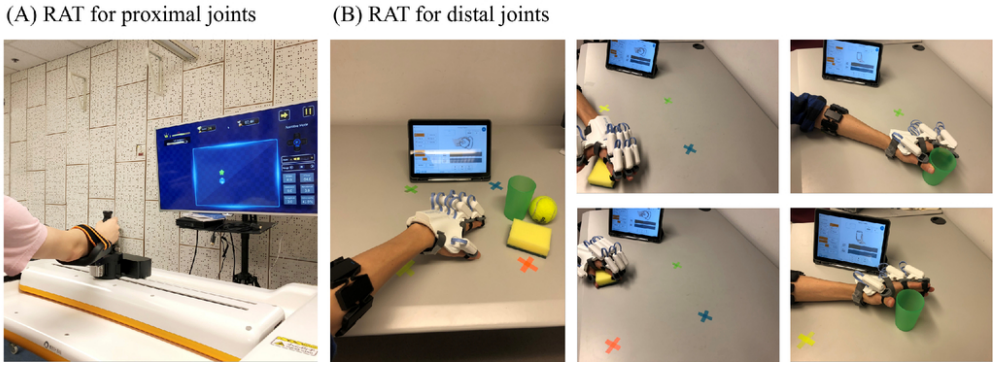

Figure 1. A demonstration of RAT. *Note The persons depicted are not patient and were taken with the participants knowledge.

87x32mm (300 x 300 DPI)

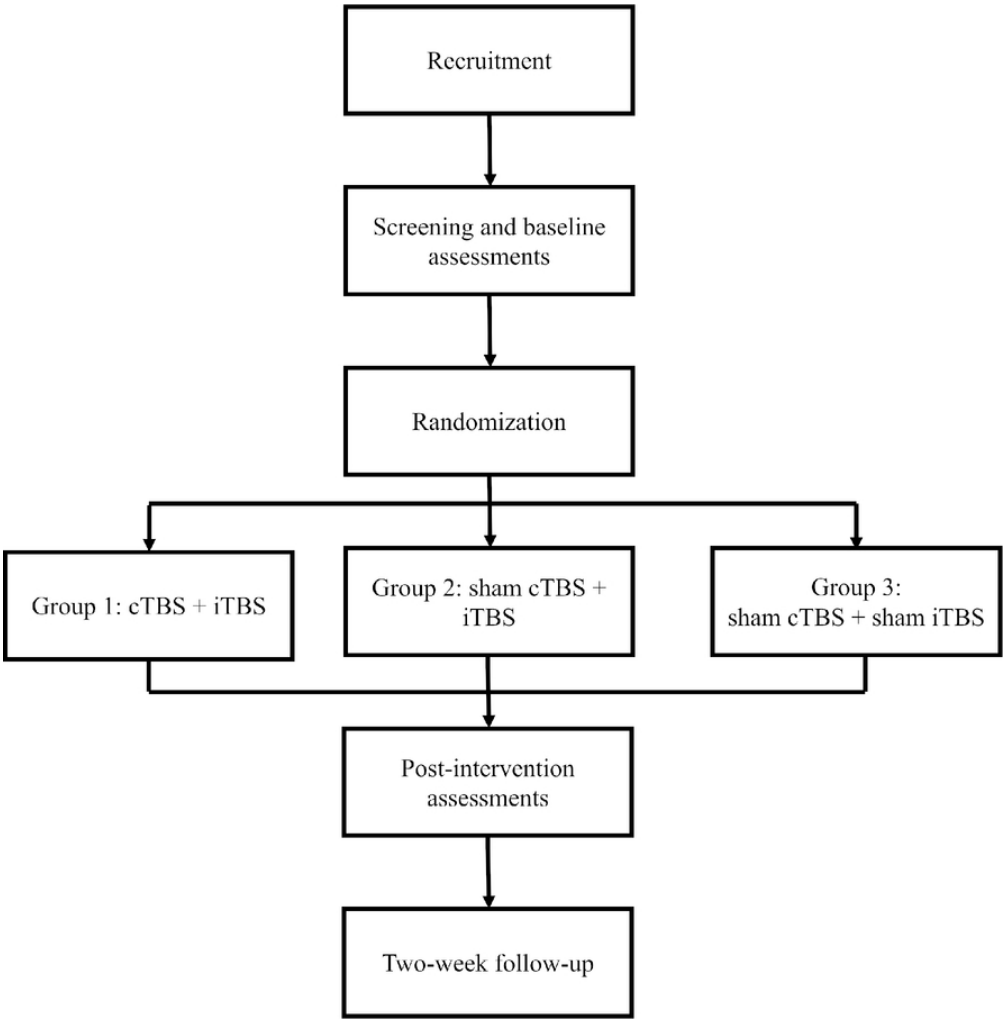

Figure 2. Flowchart of the proposed randomized controlled trial.

75x76mm (300 x 300 DPI)

Timepoint	-T1 (Screening)	T0 (Baseline)	T1 (Mid)	T2 (Post)	T3 (Follow-up)
Recruitment	X				
Eligibility screening	X				
Informed consent	X				
Randomization		X			
Intervention					
Group 1: cTBS + iTBS combined with RAT		●	———	●	
Group 2: sham cTBS + iTBS combined with RAT		●	———	●	
Group 3: Sham cTBS + sham iTBS combined with RAT		●	———	●	
Assessments					
FMA-UE	X		X	X	X
ARAT	X		X	X	X
Side-effects questionnaire		X	X	X	
Kinematic outcomes		X	X	X	
EEG		X		X	

Figure 3. Schedule of participant recruitment, assessments, and intervention. Abbreviation: iTBS: intermittent theta burst stimulation; RAT: robot-assisted training; FMA-UE: Fugl-Meyer Assessment-Upper Extremity scores; ARAT: action research arm test; EEG: electroencephalography.

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Supplementary section

The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke: Study Protocol for a Randomized Controlled Trial

Jack J.Q. ZHANG and Kenneth N.K. FONG

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University,

Kowloon, Hong Kong SAR, China

Table S1. Trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04034069
Date of registration in primary registry	First posted: July 26, 2019 Late Update: October 18. 2019
Secondary identifying numbers	HSEARS20190718003
Source(s) of monetary or material support	The Hong Kong Polytechnic University Department of Rehabilitation Sciences
Primary sponsor	The Hong Kong Polytechnic University Department of Rehabilitation Sciences
Secondary sponsor(s)	No applicable
Contact for public queries	Jack J.Q. ZHANG, MSc Email: 17902718r@connect.polyu.hk
Contact for scientific queries	Jack J.Q. ZHANG, MSc Email: 17902718r@connect.polyu.hk Kenneth. N.K. FONG, PhD Email: rsnkfong@polyu.edu.hk

Public title	The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke
Scientific title	The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke
Countries of recruitment	Hong Kong SAR, China
Health condition(s) or problem(s) studied	Stroke
Intervention(s)	Active comparator: cTBS + iTBS, in addition to robot-assisted training
	Active comparator: Sham cTBS + iTBS, in addition to robot-assisted training
	Placebo comparator: Sham cTBS + sham iTBS, in addition to robot-assisted training
Key inclusion and exclusion criteria	Ages eligible for study: 18-75 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: Chronic stroke patients (1 to 6

	years after stroke onset), with upper limb impairment (FTUHK from 2 to 7).
	Exclusion criteria: Not free of TMS contraindications; primary neurological disease excluding stroke, notable cognitive impairment (AMT < 6), extreme spasticity in any hemiplegic upper limb (MAS > 2)
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: single-blinded (outcomes assessor)
	Primary purpose: intervention
Date of first enrolment	September 2019
Target sample size	36
Recruitment status	Recruiting
Primary outcome(s)	FMA-UE and ARAT
Key secondary outcomes	Kinematic metrics (i.e., size of active range of motion, mean velocity, hand path ratio)

Abbreviations: cTBS: Continuous Theta Burst Stimulation; iTBS: Intermittent Theta Burst Stimulation; AMT: Abbreviated Mental Test; MAS: Modified Ashworth Scale; FMA-UE: Fugl-Meyer Assessment - Upper Extremity Scores; ARAT: Action Research Arm Test

Appendix: Template of written consent form

Research Consent Form
The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Title of research project:
The Effects of Priming Intermittent Theta Burst Stimulation (iTBS) on Upper Limb Motor Recovery After Stroke: A Randomized Controlled Trial

Research setting:
Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Research investigator:
Mr. Jack J.Q. Zhang (PhD candidate, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)
Dr. Kenneth N.K. Fong (Associate Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)

The purpose of this study is to investigate whether priming iTBS can enhance the therapeutic response to robot-assisted training for rehabilitating the hemiplegic upper limb functions in stroke patients. Participants need complete 10 training sessions. During each training session, participants will receive two sessions of transcranial magnetic stimulation in a form of theta burst stimulation (TBS). Immediately after the brain stimulation, participants will perform motor training assisted by robotic devices. Assessment for hemiplegic upper limb functions will be conducted in baseline, after 5-session, after 10-session and two weeks follow up. Some participants will be invited to join EEG examinations

Benefits for participants and society
The study will provide preliminary evidence of the effect of priming iTBS on stroke rehabilitation and its neural mechanisms. By participating in this study, you can receive several sessions of upper limb motor training and you do not have to pay any additional research-related payment. After the completion of 10-session of training, you will receive a transportation allowance of HK$100. For participants who join the EEG examinations, additional HK$400 will be paid as a compensation of time.

Potential risks

Although TBS is safe for most people, there may be unnecessary risks for some people. We need screen whether the participants have implanted metal objects, such as cardiac pacemakers, surgical aneurysm stents, artificial cochlear implants, or pregnancy. Before TBS, the participants should remove all metal objects on the body, such as hearing aids, dentures, orthopedic frames, watches, glasses, jewelry, any metal object on clothes, etc. In addition, it is very rare that TBS may induce seizure. Participants with a seizure/epilepsy history will not be included for this study. Other adverse effects include mild headaches and discomfort, mild cognitive or psychiatric symptoms (mild depression or mania). When strictly following the safety guidelines, those adverse effects are extremely rare.

Data confidentiality

Every participant has the right to obtain his or her personal data and publicly reported research results, if needed. According to the Law in Hong Kong (in particular the Personal Data (Privacy) Ordinance, Chapter 486), you have the right to keep your personal data confidential, such as any collection, storage, reservation, management, control and use (analysis/comparison) regarding the personal data. The information will not be transferred in Hong Kong and other places. If you have any questions, you can consult the Office of the Privacy Commissioner for Personal Data or contact their office (telephone number: 2827 2827) to properly supervise or supervise your personal data protection so that you can fully understand the meaning of legal protection of privacy information.

After agreeing to participate in the study, you authorize the following:

• In order to monitor this study, you need authorize the principal investigator and his or her research team and research ethics committee to obtain, use and retain your personal data in the manner specified in this study and this consent form, and

• In order to check and verify the completeness of the research data and reach the consistency between research regulations and any relevant requirements, you need authorize relevant government agencies (such as the Hong Kong Department of Health, Hospital Authority) to obtain your personal data

Voluntary participation:

Your participation in this research program is entirely voluntary. You may choose not to participate or may stop participating in this study at any time without any changes or loss of medical care that you accept now and in the future.

New information

If there is any new information about the study that will affect your decision to continue participating in this study, you will be notified in first time. You will be notified during the study if there are significant changes in this study that can influence your health or your willingness to participate in the study. You may have to sign a new consent form to indicate that you have been informed of new information about the study.

Exit and termination of this study

You are free to decide whether or not to participate in the study, and you may withdraw your consent at any time during the course of the study and withdraw from the study without giving any reason. It will not cause any unpleasantness or affect the medical care of your doctors in the future. The research principle investigator may also suspend the study when it is necessary. If no special request is made to destroy the data collected prior to the drop out, we will continue to use it. Participants will be given enough time to consider whether to participate in the study.

Study results

The results of this study may be published in medical journals or at medical conferences. Information related to your identity will not appear in any publicly available reports related to this study.

Contact person

If you need further information, you can contact the research investigators -- Mr. Jack J.Q, ZHANG at 65261304 or Dr. Nai Kuen Kenneth FONG, Department of Rehabilitation Sciences, Hong Kong Polytechnic University, 27666716.

If you have any questions about the rights enjoyed as a research participant, you can contact Ms. Chung (Secretary of the Research Committee of the Department of Rehabilitation Sciences, The Hong Kong Polytechnic University) at 27664329.

Your participation in this study will require you to sign and keep a copy of the consent form.

Consent form

Title of research project: The Effects of Priming Intermittent Theta Burst Stimulation (iTBS) on Upper Limb Motor Recovery After Stroke: A Randomized Controlled Trial

1. I am sure that I have read and understood the information sheet of the above research study (and I have the opportunity to ask any question about this study.

2. I understand that some of my current medical records may be checked by researchers at the Hong Kong Polytechnic University. I therefore allow these researchers to check my records.

3. I agree to use the data collected in this study for stroke research. I allow the data yielded from this study to be used for publication. I understand that my identity will be treated confidentially. Any shared and published data will be completely anonymous, so I will not be identified.

4. I understand that my participation is voluntary, and I am free to withdraw at any time without any reason. The medical care or legal rights I accept now and, in the future, will not be affected.

5. My signature of this informed consent does not mean that I waive any legal rights.

6. I agree to participate in the above research projects.

7. I understand that I will get a copy of this consent form.

_____	_____	_____
Participant name	Signature	Date
_____	_____	_____
Witness name (If applicable)	Signature	Date
_____	_____	_____
Researcher name	Signature	Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Supplementary section Table S1
Protocol version	#3	Date and version identifier	Supplementary section Table S1
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1; 22
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplementary section Table S1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplementary section Table S1

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-15
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11-15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11-15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	15-20

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a	11

		separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	16

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	21-22
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary section Table S1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke: Study Protocol for a Proof-of-Concept Randomized Controlled Trial

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Stroke < NEUROLOGY, REHABILITATION MEDICINE, NEUROLOGY

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The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke: Study Protocol for a Proof-of-Concept Randomized Controlled Trial

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Abstract

Introduction: Intermittent Theta Burst Stimulation (iTBS), a form of repetitive Transcranial Magnetic Stimulation (rTMS), delivered to the ipsilesional primary motor cortex (M1), appears to enhance the brain's response to rehabilitative training in patients with stroke. However, its clinical utility is highly subject to variability in different protocols. New evidence has reported that preceding iTBS, with continuous theta burst stimulation (cTBS) may stabilize and even boost the facilitatory effect of iTBS on the stimulated M1, via metaplasticity. The aim of this study is to investigate the effects of iTBS primed with cTBS (i.e., priming iTBS), in addition to robot-assisted training (RAT), on the improvement of the hemiparetic upper limb functions of stroke patients, and to explore potential sensorimotor neuroplasticity using electroencephalography (EEG).

Methods and analysis: A three-arm, subjects and assessors-blinded, randomized controlled trial (RCT) will be performed with patients with chronic stroke. An estimated sample of 36 patients will be needed based on the prior sample size calculation. All participants will be randomly allocated to receive 10 sessions of rTMS with different TBS protocols (cTBS+iTBS, sham cTBS+iTBS, and sham cTBS+sham iTBS), three to five sessions per week, for two to three weeks. All participants will receive 60 minutes of RAT after each stimulation session. Primary outcomes will be assessed using Fugl-Meyer Assessment – Upper Extremity scores and Action Research Arm Test.

Secondary outcomes will be assessed using kinematic outcomes generated during RAT, and EEG.

Ethics and dissemination: Ethical approval has been obtained from The Human Subjects Ethics Sub-committee, University Research Committee of The Hong Kong Polytechnic University (Reference number: HSEARS20190718003). The results yielded from this study will be presented at international conferences and sent to a peer-review journal to be considered for publication.

Trial registration number: NCT04034069.

Keywords: Theta burst stimulation; stroke; hemiparetic upper limb; priming; metaplasticity.

Article Summary

- **Strengths and limitations of this study**

· This study will be the first randomized controlled trial to explore the effects of priming iTBS in regard to facilitating hemiparetic upper limb recovery in patients with stroke.

· This study investigates sensorimotor desynchronization along with the improvement of upper limb functions, in association with priming iTBS.

· The study attempts to potentiates the brain response to iTBS by using an inhibitory priming session.

· This study contributes to the optimal use of TBS in poststroke upper limb rehabilitation.

· This study has limited generalizability to stroke patients at the acute phase.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been extensively investigated as an add-on form of therapy for stroke rehabilitation.[1] rTMS is usually limited to frequencies of 20 Hz or less, due to safety concerns, in human studies.[2] However, in animal studies, effects on synaptic plasticity are usually induced by repeated short bursts of high-frequency (> 50 Hz) stimulation, given at a frequency from 3 to 5 Hz and known as theta burst stimulation (TBS).[3] Huang *et al*. were the first to investigate the neurophysiological effects of TBS, delivered via a magnetic stimulator, in the human primary motor cortex (M1), and demonstrated that 600-pulse intermittent theta burst stimulation (iTBS) enhanced corticomotor excitability in healthy human subjects, whereas 600-pulse continuous theta burst stimulation (cTBS) did the opposite.[4] Serial TBS sessions delivered at a relatively low intensity were subsequently investigated in stroke survivors and safety concerns regarding TBS in this population appear to be minor and rare.[5-8] Various experiments with humans have also demonstrated that TBS is able to induce neuroplastic changes of the stimulated M1 in a relatively short conditioning period (i.e., 40 seconds for standard 600-pulse cTBS and three minutes for standard 600-pulse iTBS),[9] thus reducing the time spent receiving treatment.

A substantial number of clinical trials with stroke patients have revealed that iTBS of the ipsilesional M1 significantly improves hemiplegic arm[5 6 10-12] and hand[8] motor functions, compared to sham stimulations. Similar effects have also been observed in studies using cTBS of the contralesional M1.[13 14] However, some trials have not shown any additional benefits on upper limb motor outcomes from iTBS or cTBS in stroke survivors, in contrast to sham TBS.[7 13] A recent meta-analysis showed that a pooled standardized effect size of iTBS was 0.60, while that of cTBS was 0.35 for upper limb motor outcomes in patients with stroke,[15] indicating that the increment of the excitability of the affected M1 through iTBS is critical for improving the brain's response to motor training in patients with stroke. However, substantial response variability regarding iTBS among humans may contribute to the use of different protocols among current studies,[16 17] which limits their clinical utility.

It has been shown that the history of neuronal activities is one of the major factors that could influence the brain's response to TBS.[18] Synaptic plasticity is regulated by previous neuronal activities via metaplasticity. Metaplasticity is a neuroprotective mechanism that modulates the threshold of synaptic plasticity to ensure that the neural system cannot be predominated by long-term potentiation (LTP) or long-term depression (LTD).[19] Excitatory rTMS over the M1 may be unable to facilitate

corticomotor excitability when the neuronal activities have already been elevated before stimulation, which is likely happening when patients with stroke receive extensive training before non-invasive brain stimulation.

Considering the mechanism of metaplasticity, several priming stimulation protocols, designed to incorporate a priming session followed by a stimulation session, have been investigated with healthy individuals.[20] An inhibitory priming stimulation via cTBS may ensure or even boost the facilitatory effect of subsequent excitatory stimulation sessions via iTBS. In healthy individuals, this priming protocol seems to amplify the facilitatory effect of excitatory stimulation, compared with iTBS alone, as reflected by the increased amplitude of motor evoked potential (MEP).[21-23] Metaplasticity is also significantly involved in rTMS studies for patients with neuropsychiatric disorders.[24 25] However, to date no study has investigated the effects of priming iTBS protocols in patients with stroke.

Various neurological biomarkers of stroke motor recovery have been proposed.[26] Electroencephalography (EEG), a non-invasive measure of cortical neuronal oscillation, is of great interest, because it is a relatively convenient and well-tolerated neurophysiological technique for patients with stroke. Sensorimotor event-related

desynchronization (ERD), a neurophysiological marker of sensorimotor activation, could be induced through either action observation or action execution.[27] Previously, attention has been paid to movement-related sensorimotor ERD, which has been shown to be correlated with the severity of hemiplegia in patients with stroke.[28 29] Subsequently, researchers began to investigate sensorimotor ERD induced by observing mirror visual feedback (MVF) in healthy adults and patients with stroke.[30 31] A pilot study has demonstrated that multiple sessions of iTBS appear to enhance MVF-induced sensorimotor ERD in healthy adults.[32] So far, MVF-induced sensorimotor ERD has not been used as an outcome of neuroplasticity in any clinical stroke trial in order to examine its potential as a biomarker for stroke motor recovery. Sensorimotor ERD will be used to probe cortical oscillatory activities of large number of neurons in different rhythms, during a given task (movement or movement observation). A previous study comparing the effects of TBS on MEPs and movement-related rhythmic oscillations showed that the modulatory effect of TBS was more reliable on movement-related ERD than that on MEPs.[33] The potential explanations may be that TMS-based metrics may not represent all cortical responses, reflecting exclusively those destined to the spinal cord,[33] and the magnitude of TMS-based metrics is also contaminated by the neuronal responses at subcortical and spinal levels, as well as the peripheral MEP,[34] when a suprathreshold stimulation intensity is used for the measurements. Hence, we

decide to use sensorimotor desynchronization in this study, which may provide new insight about the sensorimotor neuroplasticity in association with priming iTBS.

Therefore, our study has two objectives. First, we investigate the effects of 10 sessions of rTMS using different TBS protocols (i.e., cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS plus sham iTBS), in addition to standard robot-assisted training (RAT) for both the proximal and distal joints of the hemiparetic upper limb, delivered across three to five sessions per week for two to three weeks, on improving the hemiparetic upper limb functions of stroke survivors. Fugl-Meyer Assessment - Upper Extremity (FMA-UE) scores and Action Research Arm Test (ARAT) will be used as the primary outcome measures. Safety profiles will be systematically collected during each session of the intervention, using a standard questionnaire. Second, we investigate the effects of different TBS protocols, cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS plus sham iTBS, in addition to RAT, on upper limb kinematic outcomes yielded from each RAT session, and sensorimotor ERD induced by hemiparetic hand movement and observation of the MVF of nonparetic hand movement, in patients with stroke.

Methods

This study protocol has been written according to the Standard Protocol Items for

Randomized Trials statement.[35]

Study design

This study is designed as a three-arm, parallel group, subjects- and assessors-blinded, sham-controlled RCT. Potential participants with stroke will be recruited through convenience sampling from self-support groups in the community in Hong Kong. The study will be conducted in a local university laboratory.

Inclusion and exclusion criteria

Participants must meet all of the following criteria: (1) have a diagnosis of a unilateral ischemic or hemorrhagic first-ever stroke; (2) time after stroke onset ⩾ 6 months;[36] (3) between 18 and 64 years old; (4) reside in community dwellings; (4) with residual upper limb impairment ⩾ second level in the Functional Test for the Hemiplegic Upper Extremity (FTHUE).[37] FTHUE is a fast screening tool for upper limb functional movement, which has been used as a screening in our previous RCTs.[38 39] FTHUE levels two to four are defined as low upper limb functioning poststroke, and levels five and seven are defined as high upper limb functioning poststroke;[38] (5) able to understand simple verbal instruction and follow one-step commands; and (6) able to give informed written consent to participate in the study.

Although TBS is often regarded as safe for certain subjects, the greatest acute risk of TMS is the rare occurrence of induced seizures. Besides seizures, other risks include minor pain, such as a headache or local discomfort, minor cognitive changes, and psychiatric symptoms. In this study, patients who meet any of the following rTMS contraindications will not be included: (1) unstable medical condition; (2) history of epileptic seizures, unconsciousness, or intracranial hypertension; (3) serious heart disease; (4) pregnancy; (5) with metal implants *in vivo*, such as a pacemaker, artificial cochlear, or implant brain stimulator; (6) history of receiving a craniotomy; and (7) taking any centrally acting drugs in the recent three months.[2] To ensure safety, the participants will be under the supervision of at least one investigator who has completed training in TMS. All participants will undergo a safety screening for the potential risks of TMS to ensure they are eligible to participate in this study.[2]

In addition to TMS contraindications, participants who meet any of the following criteria will be also excluded: (1) previous diagnosis of any neurological disease excluding stroke; (2) presence of any sign of cognitive problems (Abbreviated Mental Test, Hong Kong Cantonese version < 6/10);[40] (3) patients with extreme spasticity over the elbow or wrist in the hemiparetic upper limb (Modified Ashworth score > 2),[41] or

severe pain that hinders upper limb movement; (4) other notable impairments of the upper limb not affected by stroke (e.g., a recent fracture, severe osteoarthritis, congenital upper limb deformity); (5) significant aphasia or difficulty understanding the instructions given by the investigators; (6) any sign of anxiety and/or depression screened by the Hospital Anxiety and Depression Scale (HADS), using a cut-off value of 8 in both subscales;[42] and (7) concurrent participation in upper limb rehabilitation training in a hospital, university laboratory or other rehabilitation settings, or active participation in another clinical trial.

Sample size estimation

Since the difference among the effects of priming iTBS in hemiparetic upper limb training has not been previously investigated, we have estimated the sample size based on current studies comparing iTBS and sham stimulation. A recent meta-analysis yields a pooled Cohen's d of 0.60 for a two-group design in favor of iTBS improving upper limb motor outcomes, in contrast to sham stimulation.[15] An effect size (d) of 0.60 corresponds approximately to an effect size (f) of 0.30 for a study design of three-group comparisons. An estimate of sample size for each group in a three-group design, given a power of 0.80 and a two-tailed alpha error probability of 0.05, is 27 patients in total. When considering the drop-out rate of 20%, we therefore plan to recruit 12 participants

for each group (a total of 36) for this study.

Randomization

Three parallel groups will be employed: (1) cTBS plus iTBS; (2) sham cTBS plus iTBS; and (3) sham cTBS plus sham iTBS. The collection of demographic characteristics (age, gender, education, side of hemiplegia, handedness, type of stroke, time from onset to treatment, lesion site(s)) and baseline assessments will be performed prior to randomization. Participants' medical information related to their stroke will be retrieved from the electronic clinical management system in the hospital after receiving consent. All participants will be randomly allocated in a 1:1:1 ratio to each group after the screening and baseline assessments have been carried out. A random sequence will be generated using Minimize software.[43] Participants will be pre-stratified based on their hemiparetic upper limb functioning (i.e., FTHUE high functioning *vs.* low functioning). The allocation sequence will be concealed from all investigators and assessors. Participants will receive 10 sessions of TBS intervention combined with RAT, 3 to 5 sessions per week, for two to three weeks. We decide to adopt a more flexible training schedule, because most community stroke survivors are unable to visit our laboratory on a daily basis. Similar schedule for motor training has been used in previous studies for patients with chronic stroke.[44 45]

Intervention

TBS session

A total of 10 sessions of TBS will be delivered using MagPro magnetic stimulators (MagVenture, Denmark) connected with a figure-of-eight coil. Resting motor threshold (RMT) is defined as the minimum stimulation intensity over the hot spot that could elicit a motor evoked potential (MEP) of no less than 50 μv in five out of ten trials over the contralesional first dorsal interosseous (FDI) muscle. The stimulation point is the hotspot mirrored over the midsagittal line (i.e., ipsilesional M1), verified and maintained by a TMS-navigation system (Localite, Bonn, Germany).

We follow the standard 600-pulse TBS protocol proposed by Huang *et al.*[4]: iTBS: 20 trains of 10 bursts given with eight-second intervals, with a total of 600 pulses, around 3-minute per session; cTBS: 20 trains of 10 bursts given with 0.2-second intervals, with a total of 600 pulses, around 40 seconds per session. All stimulations will be delivered over the ipsilesional M1. The intensity of the TBS will be set at 70% RMT. Sham cTBS will be delivered with the same coil, but the intensity will be reduced to 20% of the individual RMT. Intensity reduction has been used as sham stimulation in some previous clinical studies,[5 46] and our pilot study.[32] The interval between the priming

session and the conditioning session will be 10 minutes.[21 25] All participants will be informed that TBS is delivered in a subthreshold intensity that cannot induce significant limb movement or somatosensory perception.

Robot-assisted training

Participants will be required to undergo two forms of RAT for the proximal and distal joints of the hemiparetic upper limb, respectively, after each TBS session. RAT will commence five minutes after the completion of the TBS session.[11] A Fourier M2 robot (Fourier Intelligence Company Limited., Shanghai, China) will be used for the upper limb proximal joint training. The Fourier M2 robot is an end-effector robot-assisted upper limb rehabilitation device, supported by tailored interactive television games in the device. A HandyRehab hand robot (Zunosaki Company Limited., Hong Kong SAR, China) will be used for upper limb distal joint training. The device provides power-driven extension and grasping force to the fingers and thumb in order to assist the patient with opening and closing the paretic hand by means of surface electromyography (EMG) triggered from the signals through the forearm extensors and flexors. Active and passive modes are available in both robots. Whenever patients are unable to use the active modes due to the severity of the upper limb hemiplegia, passive modes will be used.

Proximal joint training

The Fourier M2 robot targets (1) flexion and extension of the shoulder joint; (2) flexion and extension of the elbow; (3) internal and external rotation of the shoulder joint; and (4) abduction and adduction of the shoulder joint. Before each training session, the size of the maximal active range of motion (ROM) for the hemiplegic upper limb will be assessed for each participant. Two-minute warm-up sessions will be delivered before and after each training session, in which participants will receive passive-mode RAT to mobilize the paretic upper limb. The movement trajectory will be predefined as a square and its size will be calculated based on participants' maximal active ROM. In the training session, the participants will be asked to move their hemiparetic upper limb to reach sequentially presented targets in an interactive game. Each proximal joint training session will last for around 30 minutes, with a break of five to 10 minutes (see Figure 1A for a demonstration of proximal joint RAT). The assistive mode will be used to train the patients with limited voluntary shoulder and elbow movement (i.e., the patient initiates the movement and the robot then produces assistive force according to the subject's effort). For patients who cannot initiate movement by themselves, the passive mode will be used. The active mode and resistive mode will be used to train the patients with voluntary shoulder and elbow movement. Each participant has to sit in front of the

robot with a computer screen attached to the device. The participant will wear a trunk-fixed belt to minimize compensatory movement of the trunk during training.

Distal joint training

The HandyRehab hand robot is lightweight, powered by lithium batteries, and allows the subject to perform a full hand grasp/release movement in either the spherical grip or cylindrical grip mode. The EMG trigger threshold will be adjusted based on patients' hemiplegic arm function. Participants will be instructed to perform the different types of hand movements to pick up an object (i.e., a ball, sponge, or a cup) on a table, move it vertically and/or horizontally to four predefined targets, and release the object. The distance between the targets and participants will be adjusted based on their active ROM of proximal joints in the paretic upper limb. The EMG-triggered level will be adjusted based on patients' ability (i.e., active mode) and gradually increased as the training progresses. For patients without any detectable EMG signal from the paretic forearm, the passive mode will be used. Each distal joint training session will last for around 30 minutes, with a break of five to 10 minutes (see Figure 1B for a demonstration of distal joint RAT). In total, each RAT session lasts for approximately 60 minutes (30 minutes for proximal joints and 30 minutes for distal joints), with 10 sessions in total. An investigator with a background in physiotherapy or occupational

therapy will supervise each participant during each robot training session to ensure the correct positioning is used and that and participants become familiar with the training.

Outcome measurements

Primary outcomes

The FMA-UE and ARAT will be used as the primary outcomes for this study.[47] The FMA-UE is a clinical assessment for upper limb motor impairment after stroke. It includes 33 items assessing the movement, coordination, and reflex actions of the shoulder, elbow, forearm, and wrist, and the hand joints of the paretic arm. Each item consists of a three-point scale (zero, one, and two), with a total maximum score of 66. The minimal clinically important difference (MCID) of the FMA-UE is 5.25 points.[48] The FMA-UE will be conducted at four time points: baseline, mid-term (i.e., after five sessions), post-training (i.e., after 10 sessions), and follow-up (i.e., two weeks after the completion of all training sessions). An assessor who is unaware of the treatment allocation will carry out the assessment for each participant. The ARAT is a clinical assessment for upper limb functional activities for patients with stroke. The ARAT assesses proximal and distal components of upper limb function. It consists of four subscales: grasp, grip, pinch, and gross movement. It has 19 movement tasks, each graded using a four-point scale (total scores range from 0 to 57). The MCID of ARAT

is 5.70 points.[49] ARAT will be conducted at the same four time points as the FMA-UE. An assessor who is unaware of the treatment allocation will carry out the assessment for each participant. Assessors will be trained and tested by the principle investigator, before conducting clinical assessments.

Secondary outcomes

Kinematic metrics generated during each session of RAT will be used as secondary outcomes for the participants' upper limb function. The following kinematic metrics retrieved from the M2 robot will be used as the upper limb motor outcomes in a further analysis: (1) the size of the maximal active ROM; (2) the mean velocity of movement during the training session; and (3) the movement trajectory during the training session. Movement trajectory will be further calculated as the hand-path ratio, which is defined as the real distance divided by the shortest distance between object targets.[50]

In order to investigate the potential neuroplasticity elicited by the training, we will invite patients to participate in EEG examinations. We expect that around five patients from each group will take part in the EEG examinations before and after the intervention. Kinematic and EEG outcomes will be assessed in a non-blinded manner (see Figure 2 for a flowchart).

EEG acquisition

EEG will be captured with a 64-channel cap using a Digital DC EEG Amplifier. Electrode impedance will be kept below 10 kOhm and the signal will be sampled at 1000 Hz. Movement-related ERD and MVF-induced ERD will be evaluated in this study. For movement-related ERD, participants will be asked to perform finger taps three times (or attempt to move their finger if they cannot perform the movement fluently) on a computer keyboard with the index finger of their unaffected side, in response to auditory cues (i.e., a 300-ms beep sound) delivered at random intervals (from seven seconds to 10 seconds), and to relax their hand after the completion of the movement.

For MVF-induced ERD, participants will be asked to perform finger taps three times on a computer keyboard with the index finger of their unaffected side, in response to auditory cues delivered at random intervals (from seven seconds to 10 seconds),[51] and to relax their hand after the completion of the movement. A widely used EEG paradigm exploring the effects of MVF will be utilized in the present study;[30-32 51 52] movements will be performed under two conditions. (1) MVF of the hand movement: Participants will be required to perform unilateral finger tapping while viewing MVF. MVF will be

created using a physical mirror (406 × 432 mm) placed over their midsagittal plane, between both arms. (2) Direct visual feedback (DVF) of the hand movement: Participants will be required to perform unilateral finger tapping while directly looking at their moving finger. The affected hand will be hidden by a non-reflective board.

The order of conditions will be allocated randomly by drawing lots. A total of 60 movements will be collected for each condition (affected index movement, unaffected index with mirror view, and unaffected index with direct view), with 180 movements in total.

EEG preprocessing

Raw EEG signals will be band-pass filtered between 1 and 80 Hz and then down-sampled at 250 Hz. Additionally, a 50-Hz notch filter will be applied. Data will be offline re-referenced to bilateral mastoid electrodes. Signals with significant movement artifacts and long-term eye closure will be rejected during a visual inspection. Subsequently, EEG will be segmented in 7000 ms epochs (pre-stimulus -3000 ms and post-stimulus 4000 ms, with 0 as the first finger tap). Eye movement artifacts will be corrected using an independent component analysis algorithm.[53] Typical components reflecting the eye blinks and horizontal movements will then be rejected.

EEG time-frequency analysis

Clean epochs will be analyzed in a time-frequency domain. The event-related spectral perturbation (ERSP) method using the *newtimef* function of EEGLAB[54] will be used to compute the ERD power. The ERD power will be baseline corrected. Subsequently, the power will be averaged across all trials and converted to log power. Averaged ERD powers at electrode sites C3 (ipsilesional hemisphere, IH) and C4 (contralesional hemisphere, CH) will be extracted. Data from patients with right brain lesions will be flipped to ensure that C3 channels stand for IHs and C4 channels stand for CHs.

For movement-related ERD, the power at C3 will be used for further analysis. For MVF-induced ERD, the powers at IH and CH during the movement phase will be extracted and an asymmetric index will be calculated with the following formula:[55]

$$\text{Asymmetric index} = (\text{IH ERD power}) - (\text{CH ERD power})$$

The difference of asymmetric indices under the mirror view and direct view will be used to evaluate MVF-induced sensorimotor ERD and used in a further analysis. A more negative value indicates more activation toward the ipsilesional sensorimotor area,

during the mirror view condition, compared to the direct view condition. Mu-1 (8-10 Hz), mu-2 (10-12 Hz), beta-1 (12-16 Hz), and beta-2 (16-30 Hz) will be investigated separately.[32]

Safety profile investigation

A side-effects survey will be distributed upon completion of each TBS session. See Figure 3 for an overview of the proposed trial.

Statistical Analysis

Statistical analysis will be performed using SPSS version 23.0. Demographic and baseline characteristics will be compared using analysis of variance (ANOVA; continuous and ordinal data) or Chi-square tests (categorical data). A mixed-effects model with random intercepts and slopes will be used to detect any significant differences in the rate of change in motor outcomes and sensorimotor ERD among the three groups, because of its superiority in analyzing repeated measures data and dataset with missing values. Any factor with significant between-group difference in the baseline will be included in the mixed-effects model as covariates. Group effects, time effects, and group-by-time interaction effects will be included as fixed effects, and the random intercept and random slope of change in the dependent variables over time will

be included as random effects. Between-group differences will be investigated using the interaction effects. Maximum likelihood estimation will be chosen as the estimation method. The covariance structure is assumed to be unstructured. The level of significance will be set at $p < 0.05$. For post-hoc comparisons, the level of significance will be set at $p < 0.017$ after Bonferroni adjustment (0.05/3; n = number of comparisons), for the comparison of interaction effects. Cohen's d will be calculated to determine the effect size of the change scores for the behavioral motor outcomes between groups. Immediate training effects (data from baseline to post-training) and the durability of training effects (data from post-training to follow-up) will be separately investigated with mixed-effect models. Frequency scores for each reported side effect and the percentage of participants who pass the MCID of the FMA-UE and ARAT will be compared using Chi-squared tests between the three groups.

Patient and public involvement

Patients will be invited to participate in this study via advertisements. Several self-help stroke organizations will be notified in order to promote the enrollment. The results of the evaluation can be released to participants upon request.

Ethics and dissemination

This randomized controlled trial was registered on 24 July 2019 (https://clinicaltrials.gov, see supplementary section for trial registration data). The study has launched on 9th September 2019 and will continue for around a year. The study will be conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent forms will be collected from each participant before the study begins (see a template of written consent form in supplementary section). Ethical consideration has been approved from the human subject ethics subcommittee of the Hong Kong Polytechnic University. Any modifications to this study protocol will also be reviewed by the subcommittee. This study will only include participants who have given informed written consent and the confidentiality is assured. All original data will be kept in strictly private. During the study, written data will be stored in a safe place; after the study, all data will be input to a computer by the principle investigator and a backup of the data will be kept on a hard drive, which will be stored in a safe place. The input data will be double checked by another research assistant. Personal data will be discarded after three years. Due to the small expected sample size of this proof-of-concept study, a data monitoring committee was not deemed to be required and we will perform interim analyses when 50% of patients have been included and have completed the follow-up assessment. . The results of this study will be presented at international conferences and sent to a peer-reviewed journal to be considered for publication.

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Figure Legends

Figure 1. A demonstration of RAT.

*Note: The persons depicted are not patient and were taken with the participants knowledge.

Figure 2. Flowchart of the proposed randomized controlled trial.

Figure 3. Schedule of participant recruitment, assessments, and intervention. Abbreviation: iTBS: intermittent theta burst stimulation; RAT: robot-assisted training; FMA-UE: Fugl-Meyer Assessment-Upper Extremity scores; ARAT: action research arm test; EEG: electroencephalography.

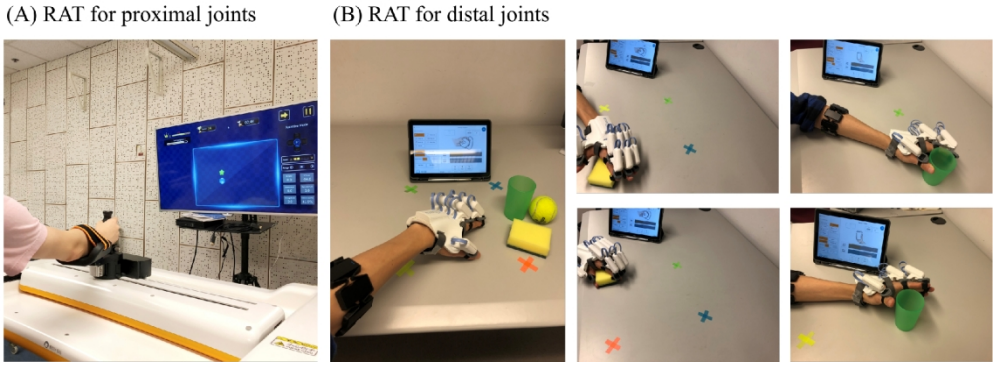

Figure 1. A demonstration of RAT. *Note The persons depicted are not patient and were taken with the participants knowledge.

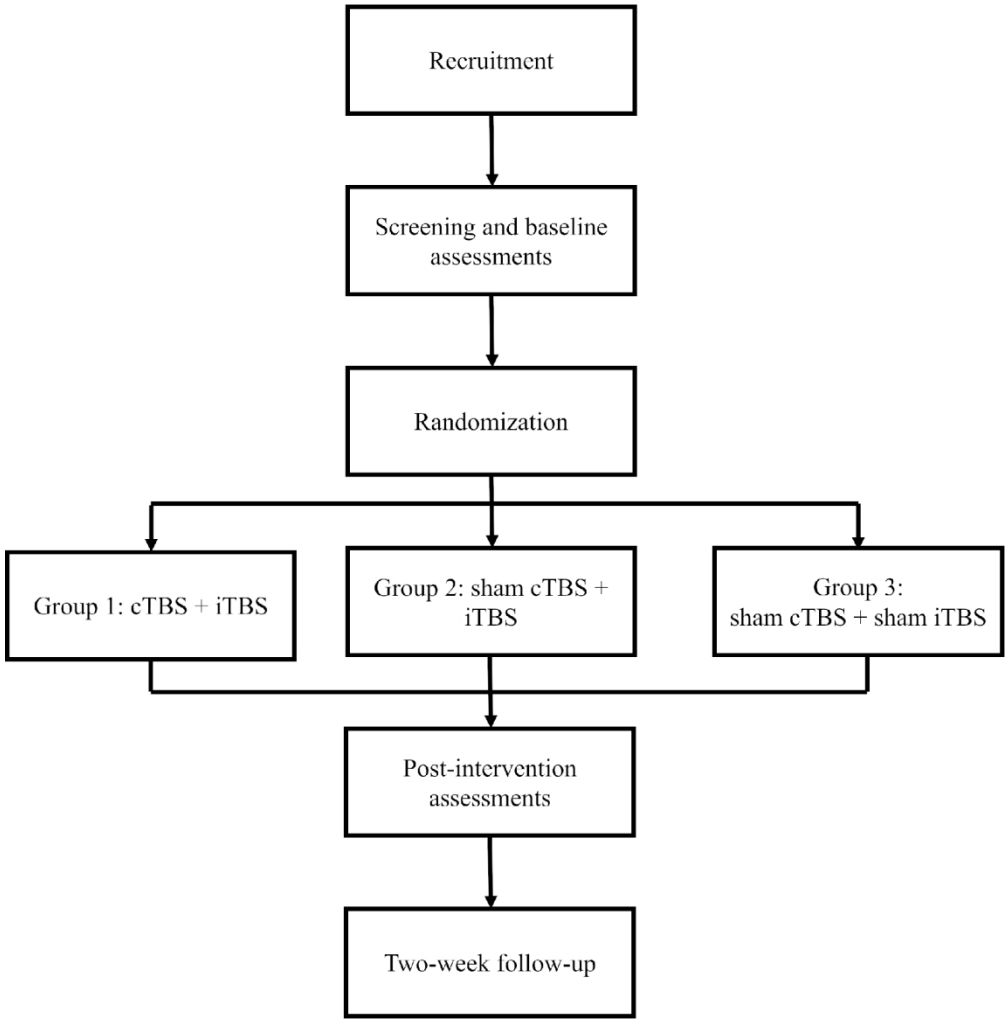

Figure 2. Flowchart of the proposed randomized controlled trial.

Timepoint	-T1 (Screening)	T0 (Baseline)	T1 (Mid)	T2 (Post)	T3 (Follow-up)
Recruitment	X				
Eligibility screening	X				
Informed consent	X				
Randomization		X			
Intervention					
Group 1: cTBS + iTBS combined with RAT		●	———	●	
Group 2: sham cTBS + iTBS combined with RAT		●	———	●	
Group 3: Sham cTBS + sham iTBS combined with RAT		●	———	●	
Assessments					
FMA-UE	X		X	X	X
ARAT	X		X	X	X
Side-effects questionnaire		X	X	X	
Kinematic outcomes		X	X	X	
EEG		X		X	

Figure 3. Schedule of participant recruitment, assessments, and intervention. Abbreviation: iTBS: intermittent theta burst stimulation; RAT: robot-assisted training; FMA-UE: Fugl-Meyer Assessment-Upper Extremity scores; ARAT: action research arm test; EEG: electroencephalography.

Supplementary Section

The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke: Study Protocol for a Proof-of-Concept Randomized Controlled Trial

Jack Jiaqi ZHANG and Kenneth N.K. FONG

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University,

Kowloon, Hong Kong SAR, China

Table S1. Trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04034069
Date of registration in primary registry	First posted: July 26, 2019 Late Update: October 18. 2019
Secondary identifying numbers	HSEARS20190718003
Source(s) of monetary or material support	The Hong Kong Polytechnic University Department of Rehabilitation Sciences
Primary sponsor	The Hong Kong Polytechnic University Department of Rehabilitation Sciences
Secondary sponsor(s)	No applicable
Contact for public queries	Jack Jiaqi ZHANG, MSc Email: 17902718r@connect.polyu.hk
Contact for scientific queries	Jack Jiaqi ZHANG, MSc Email: 17902718r@connect.polyu.hk Kenneth N.K. FONG, PhD Email: rsnkfong@polyu.edu.hk

Public title	The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke
Scientific title	The Effects of Priming Intermittent Theta Burst Stimulation on Upper Limb Motor Recovery After Stroke
Countries of recruitment	Hong Kong SAR, China
Health condition(s) or problem(s) studied	Stroke
Intervention(s)	Active comparator: cTBS + iTBS, in addition to robot-assisted training
	Active comparator: Sham cTBS + iTBS, in addition to robot-assisted training
	Placebo comparator: Sham cTBS + sham iTBS, in addition to robot-assisted training
Key inclusion and exclusion criteria	Ages eligible for study: 18-64 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: Chronic stroke patients (⩾ 6

	months after stroke onset), with upper limb impairment (FTUHK from 2 to 7).
	Exclusion criteria: Not free of TMS contraindications; primary neurological disease excluding stroke, notable cognitive impairment (AMT < 6), extreme spasticity in anyhemiplegic upper limb (MAS > 2)
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: single-blinded (outcomes assessor)
	Primary purpose: intervention
Date of first enrolment	September 2019
Target sample size	36
Recruitment status	Recruiting
Primary outcome(s)	FMA-UE and ARAT
Key secondary outcomes	Kinematic metrics (i.e., size of active range of motion, mean velocity, hand path ratio)

Abbreviations: cTBS: Continuous Theta Burst Stimulation; iTBS: Intermittent Theta Burst Stimulation; AMT: Abbreviated Mental Test; MAS: Modified Ashworth Scale; FMA-UE: Fugl-Meyer Assessment - Upper Extremity Scores; ARAT: Action Research Arm Test

Appendix: Template of written consent form

Research Consent Form
The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Title of research project:
The Effects of Priming Intermittent Theta Burst Stimulation (iTBS) on Upper Limb Motor Recovery After Stroke: A Randomized Controlled Trial

Research setting:
Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Research investigator:
Mr. Jack Jiaqi Zhang (PhD candidate, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)
Dr. Kenneth N.K. Fong (Associate Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)

The purpose of this study is to investigate whether priming iTBS can enhance the therapeutic response to robot-assisted training for rehabilitating the hemiplegic upper limb functions in stroke patients. Participants need complete 10 training sessions. During each training session, participants will receive two sessions of transcranial magnetic stimulation in a form of theta burst stimulation (TBS). Immediately after the brain stimulation, participants will perform motor training assisted by robotic devices. Assessment for hemiplegic upper limb functions will be conducted in baseline, after 5-session, after 10-session and two weeks follow up. Some participants will be invited to join EEG examinations

Benefits for participants and society
The study will provide preliminary evidence of the effect of priming iTBS on stroke rehabilitation and its neural mechanisms. By participating in this study, you can receive several sessions of upper limb motor training and you do not have to pay any additional research-related payment. After the completion of 10-session of training, you will receive a transportation allowance of HK$100. For participants who join the EEG examinations, additional HK$400 will be paid as a compensation of time.

Potential risks

Although TBS is safe for most people, there may be unnecessary risks for some people. We need screen whether the participants have implanted metal objects, such as cardiac pacemakers, surgical aneurysm stents, artificial cochlear implants, or pregnancy. Before TBS, the participants should remove all metal objects on the body, such as hearing aids, dentures, orthopedic frames, watches, glasses, jewelry, any metal object on clothes, etc. In addition, it is very rare that TBS may induce seizure. Participants with a seizure/epilepsy history will not be included for this study. Other adverse effects include mild headaches and discomfort, mild cognitive or psychiatric symptoms (mild depression or mania). When strictly following the safety guidelines, those adverse effects are extremely rare.

Data confidentiality

Every participant has the right to obtain his or her personal data and publicly reported research results, if needed. According to the Law in Hong Kong (in particular the Personal Data (Privacy) Ordinance, Chapter 486), you have the right to keep your personal data confidential, such as any collection, storage, reservation, management, control and use (analysis/comparison) regarding the personal data. The information will not be transferred in Hong Kong and other places. If you have any questions, you can consult the Office of the Privacy Commissioner for Personal Data or contact their office (telephone number: 2827 2827) to properly supervise or supervise your personal data protection so that you can fully understand the meaning of legal protection of privacy information.

After agreeing to participate in the study, you authorize the following:

• In order to monitor this study, you need authorize the principal investigator and his or her research team and research ethics committee to obtain, use and retain your personal data in the manner specified in this study and this consent form, and

• In order to check and verify the completeness of the research data and reach the consistency between research regulations and any relevant requirements, you need authorize relevant government agencies (such as the Hong Kong Department of Health, Hospital Authority) to obtain your personal data

Voluntary participation:

Your participation in this research program is entirely voluntary. You may choose not to participate or may stop participating in this study at any time without any changes or loss of medical care that you accept now and in the future.

New information

If there is any new information about the study that will affect your decision to continue participating in this study, you will be notified in first time. You will be notified during the study if there are significant changes in this study that can influence your health or your willingness to participate in the study. You may have to sign a new consent form to indicate that you have been informed of new information about the study.

Exit and termination of this study

You are free to decide whether or not to participate in the study, and you may withdraw your consent at any time during the course of the study and withdraw from the study without giving any reason. It will not cause any unpleasantness or affect the medical care of your doctors in the future. The research principle investigator may also suspend the study when it is necessary. If no special request is made to destroy the data collected prior to the drop out, we will continue to use it. Participants will be given enough time to consider whether to participate in the study.

Study results

The results of this study may be published in medical journals or at medical conferences. Information related to your identity will not appear in any publicly available reports related to this study.

Contact person

If you need further information, you can contact the research investigators -- Mr. Jack Jiaqi ZHANG at 65261304 or Dr. Kenneth N.K. FONG, Department of Rehabilitation Sciences, Hong Kong Polytechnic University, 27666716.

If you have any questions about the rights enjoyed as a research participant, you can contact Ms. Chung (Secretary of the Research Committee of the Department of Rehabilitation Sciences, The Hong Kong Polytechnic University) at 27664329.

Your participation in this study will require you to sign and keep a copy of the consent form.

Consent form

Title of research project: The Effects of Priming Intermittent Theta Burst Stimulation (iTBS) on Upper Limb Motor Recovery After Stroke: A Randomized Controlled Trial

1. I am sure that I have read and understood the information sheet of the above research study (and I have the opportunity to ask any question about this study.
2. I understand that some of my current medical records may be checked by researchers at the Hong Kong Polytechnic University. I therefore allow these researchers to check my records.
3. I agree to use the data collected in this study for stroke research. I allow the data yielded from this study to be used for publication. I understand that my identity will be treated confidentially. Any shared and published data will be completely anonymous, so I will not be identified.
4. I understand that my participation is voluntary, and I am free to withdraw at any time without any reason. The medical care or legal rights I accept now and, in the future, will not be affected.
5. My signature of this informed consent does not mean that I waive any legal rights.
6. I agree to participate in the above research projects.
7. I understand that I will get a copy of this consent form.

Participant name	Signature	Date
Witness name (If applicable)	Signature	Date
Researcher name	Signature	Date

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Supplementary section Table S1
Protocol version	#3	Date and version identifier	Supplementary section Table S1
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1; 26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplementary section Table S1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Supplementary section Table S1

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10-11
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-18
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14-18
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14-18
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-18
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	18-19

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	24
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a	13

		separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14-15; 18-19
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	18-19

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	24
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	23-24
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	23-24
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	23-24

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	24-25

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	24-25
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	24-25
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	24-25
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24-25
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24-25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	24-26
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24-25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary section Table S1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA