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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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**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.

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4 **Ethics and dissemination:** Ethical approval has been obtained from The Human
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6
7 Subjects Ethics Sub-committee, University Research Committee of The Hong Kong
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9
10 Polytechnic University (Reference number: HSEARS20190718003). The results
11
12
13 yielded from this study will be presented at international conferences and sent to a peer-
14
15
16 review journal to be considered for publication.

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19 (268 words)

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22 **Trial registration number:** NCT04034069.

23
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25 **Keywords:** Theta burst stimulation; stroke; hemiparetic upper limb; priming;
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28 metaplasticity.
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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

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4 the ipsilesional M1 significantly improves hemiplegic arm^{5 8 10-12} and hand⁶ motor
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7 functions, compared to sham stimulations. Similar effects have also been observed in
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10 studies using cTBS of the contralesional M1.^{13 14} However, some trials have not shown
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12
13 any additional benefits on upper limb motor outcomes from iTBS or cTBS in stroke
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16 survivors, in contrast to sham TBS.^{7 15} A recent meta-analysis showed that a pooled
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18
19 standardized effect size of iTBS was 0.60, while that of cTBS was 0.35 for upper limb
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21
22 motor outcomes in patients with stroke,¹⁶ indicating that the increment of the
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24
25 excitability of the affected M1 through iTBS is critical for improving the brain's
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28 response to motor training in patients with stroke. However, substantial response
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31 variability regarding iTBS among humans may contribute to the use of different
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33
34 protocols among current studies,^{17 18} which limits their clinical utility.

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40 It has been shown that the history of neuronal activities is one of the major factors that
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43 could influence the brain's response to TBS.¹⁹ Synaptic plasticity is regulated by
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46 previous neuronal activities via metaplasticity. Metaplasticity is a neuroprotective
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49 mechanism that modulates the threshold of synaptic plasticity to ensure that the neural
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52 system cannot be predominated by long-term potentiation (LTP) or long-term
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55 depression (LTD).²⁰ Excitatory rTMS over the M1 may be unable to facilitate
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58 corticomotor excitability when the neuronal activities have already been elevated
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4 before stimulation, which is likely happening when patients with stroke receive
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7 extensive training before non-invasive brain stimulation.
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13 Considering the mechanism of metaplasticity, several priming stimulation protocols,
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16 designed to incorporate a priming session followed by a stimulation session, have been
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19 investigated with healthy individuals.²¹ An inhibitory priming stimulation via cTBS
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22 may ensure or even boost the facilitatory effect of subsequent excitatory stimulation
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25 sessions via iTBS. In healthy individuals, this priming protocol seems to amplify the
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28 facilitatory effect of excitatory stimulation, compared with iTBS alone, as reflected by
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31 the increased amplitude of motor evoked potential (MEP).²²⁻²⁴ To the best of our
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34 knowledge, no study has investigated the effects of priming iTBS protocols in patients
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37 with stroke to date.
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43 Various neurological biomarkers of stroke motor recovery have been proposed.²⁵
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46 Electroencephalography (EEG), a non-invasive measure of cortical neuronal oscillation,
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49 is of great interest, because it is a relatively convenient and well-tolerated brain imaging
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51
52 technique for patients with stroke. Sensorimotor event-related desynchronization
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55 (ERD), a neurophysiological marker of sensorimotor activation, could be induced
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58 through either action observation or action execution.²⁶ Previously, attention has been
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4 paid to movement-related sensorimotor ERD, which has been shown to be correlated
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7 with the severity of hemiplegia in patients with stroke.^{27 28} Subsequently, researchers
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10 began to investigate sensorimotor ERD induced by observing mirror visual feedback
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12
13 (MVF) in healthy adults and patients with stroke.^{29 30} A pilot study has demonstrated
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16 that multiple sessions of iTBS appear to enhance MVF-induced sensorimotor ERD in
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19 healthy adults.³¹ So far, MVF-induced sensorimotor ERD has not been used as an
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22 outcome of neuroplasticity in any clinical stroke trial in order to examine its potential
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25 as a biomarker for stroke motor recovery.
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31 Therefore, our study has two objectives: First, we investigate the effects of 10 sessions
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34 of rTMS using different TBS protocols (i.e., cTBS plus iTBS, sham cTBS plus iTBS,
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37 and sham cTBS plus sham iTBS), in addition to standard robot-assisted training (RAT)
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40 for both the proximal and distal joints of the hemiparetic upper limb, delivered across
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43 three to five sessions per week for two to three weeks, on improving the hemiparetic
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46 upper limb functions of stroke survivors. Fugl-Meyer Assessment - Upper Extremity
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48
49 (FMA-UE) scores and Action Research Arm Test (ARAT) will be used as the primary
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52 outcome measures. Safety profiles will be systematically collected during each session
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55 of the intervention, using a standard questionnaire. Second, we investigate the effects
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58 of different TBS protocols, cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS
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4 plus sham iTBS, in addition to RAT, on upper limb kinematic outcomes yielded from
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6
7 each RAT session, and sensorimotor ERD induced by hemiparetic hand movement and
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10 observation of the MVF of nonparetic hand movement, in patients with stroke.
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16 **Methods**

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19 This study protocol has been written according to the Standard Protocol Items for
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21
22 Randomized Trials statement.³²
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28 **Study design**

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

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49 Participants must meet all of the following criteria: (1) have a diagnosis of a unilateral
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52 ischemic or hemorrhagic first-ever stroke; (2) with stroke onset of one year to six years
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55 before the study; (3) between 18 and 75 years old; (4) reside in community dwellings;
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58 (4) with residual upper limb impairment \geq second level in the Functional Test for the
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4 Hemiplegic Upper Extremity (FTHUE).³³ FTHUE levels two to four are defined as low
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7 upper limb functioning poststroke, and levels five and seven are defined as high upper
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10 limb functioning poststroke; (5) able to understand simple verbal instruction and follow
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13 one-step commands; and (6) able to give informed written consent to participate in the
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16 study.

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22 Although TBS is often regarded as safe for certain subjects, the greatest acute risk of
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25 TMS is the rare occurrence of induced seizures. Besides seizures, other risks include
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28 minor pain, such as a headache or local discomfort, minor cognitive changes, and
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31 psychiatric symptoms. In this study, patients who meet any of the following rTMS
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34 contraindications will not be included: (1) unstable medical condition; (2) history of
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37 epileptic seizures, unconsciousness, or intracranial hypertension; (3) serious heart
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39
40 disease; (4) pregnant; (5) significant aphasia or difficulty understanding the instructions
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43 given by the investigators; (6) with metal implants *in vivo*, such as a pacemaker,
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46 artificial cochlear, or implant brain stimulator; (7) history of receiving a craniotomy; or
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48
49 (8) does not consent to TBS intervention.² To ensure safety, the participants will be
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52 under the supervision of at least one investigator who has completed training in TMS.
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55 All participants will undergo a safety screening for the potential risks of TMS to ensure
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58 they are eligible to participate in this study.
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7 In addition to TMS contraindications, participants who meet any of the following
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10 criteria will be also excluded: (1) previous diagnosis of any neurological disease
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13 excluding stroke; (2) presence of any sign of cognitive problems (Abbreviated Mental
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16 Test, Hong Kong Cantonese version $< 6/10$);³⁴ (3) patients with extreme spasticity over
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19 the elbow or wrist in the hemiparetic upper limb (Modified Ashworth score > 2),³⁵ or
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21
22 severe pain that hinders upper limb movement; (4) other notable impairments of the
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25 upper limb not affected by stroke (e.g., a recent fracture, severe osteoarthritis,
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28 congenital upper limb deformity); and (5) concurrent participation in upper limb
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31 rehabilitation training in a hospital, university laboratory or other rehabilitation settings,
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34 or active participation in another clinical trial.
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40 **Sample size estimation**

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43 Since the difference among the effects of priming iTBS in hemiparetic upper limb
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46 training has not been previously investigated, we have estimated the sample size based
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49 on current studies comparing iTBS and sham stimulation. A recent meta-analysis yields
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51
52 a pooled Cohen's d of 0.60 for a two-group design in favor of iTBS improving upper
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55 limb motor outcomes, in contrast to sham stimulation.¹⁶ An effect size (d) of 0.60
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58 corresponds approximately to an effect size (f) of 0.30 for a study design of three-group
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4 comparisons. An estimate of sample size for each group in a three-group design, given
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6
7 a power of 0.80 and a two-tailed alpha error probability of 0.05, is 27 patients in total.
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10 When considering the drop-out rate of 20%, we therefore plan to recruit 12 participants
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13 for each group (a total of 36) for this study.
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19 **Randomization**

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

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4 perception.
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10 **Robot-assisted training**

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13 Participants will be required to undergo two forms of RAT for the proximal and distal
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15 joints of the hemiparetic upper limb, respectively, after each TBS session. RAT will
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17 commence five minutes after the completion of the TBS session.¹¹ A Fourier M2 robot
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19 (Fourier Intelligence Co. Ltd., Shanghai, China) will be used for the upper limb
20
21 proximal joint training. The Fourier M2 robot is an end-effector robot-assisted upper
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23 limb rehabilitation device, supported by tailored interactive television games in the
24
25 device. A HandyRehab hand robot (Zunosaki Company Limited., Hong Kong SAR,
26
27 China) will be used for upper limb distal joint training. The device provides power-
28
29 driven extension and grasping force to the fingers and thumb in order to assist the
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31 patient with opening and closing the paretic hand by means of surface
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33 electromyography (EMG) triggered from the signals through the forearm extensors and
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35 flexors. Active and passive modes are available in both robots. Whenever patients are
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37 unable to use the active modes due to the severity of the upper limb hemiplegia, passive
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39 modes will be used.
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58 **Proximal joint training**

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4 The Fourier M2 robot targets (1) flexion and extension of the shoulder joint; (2) flexion
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7 and extension of the elbow; (3) internal and external rotation of the shoulder joint; and
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9
10 (4) abduction and adduction of the shoulder joint. Before each training session, the size
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13 of the maximal active range of motion (ROM) for the hemiplegic upper limb will be
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16 assessed for each participant. Two-minute warm-up sessions will be delivered before
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19 and after each training session, in which participants will receive passive-mode RAT to
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22 mobilize the paretic upper limb. The movement trajectory will be predefined as a square
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25 and its size will be calculated based on participants' maximal active ROM. In the
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28 training session, the participants will be asked to move their hemiparetic upper limb to
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31 reach sequentially presented targets in an interactive game. Each proximal joint training
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34 session will last for around 30 minutes, with a break of five to 10 minutes (see Figure
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37 1A for a demonstration of proximal joint RAT). The assistive mode will be used to train
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40 the patients with limited voluntary shoulder and elbow movement (i.e., the patient
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43 initiates the movement and the robot then produces assistive force according to the
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46 subject's effort). For patients who cannot initiate movement by themselves, the passive
47
48
49 mode will be used. The active mode and resistive mode will be used to train the patients
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52 with voluntary shoulder and elbow movement. Each participant has to sit in front of the
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55 robot with a computer screen attached to the device. The participant will wear a trunk-
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58 fixed belt to minimize compensatory movement of the trunk during training.
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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 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

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

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22 Kinematic metrics generated during each session of RAT will be used as secondary
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25 outcomes for the participants' upper limb function. The following kinematic metrics
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28 retrieved from the M2 robot will be used as the upper limb motor outcomes in a further
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31 analysis: (1) the size of the maximal active ROM; (2) the mean velocity of movement
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34 during the training session; and (3) the movement trajectory during the training session.
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37 Movement trajectory will be further calculated as the hand-path ratio, which is defined
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40 as the real distance divided by the shortest distance between object targets.⁴¹
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47 In order to investigate the potential neuroplasticity elicited by the training, we will
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49 invite patients to participate in EEG examinations. We expect that around five patients
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52 from each group will voluntarily take part in the EEG examinations before and after the
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55 intervention. For participants who participate the EEG part, 400 Hong Kong dollars
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58 will be paid as an incentive. Kinematic and EEG outcomes will be assessed in a non-
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4 blinded manner (see Figure 2 for a flowchart).
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10 **EEG acquisition**

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12 EEG will be captured with a 64-channel cap using a Digital DC EEG Amplifier.
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16 Electrode impedance will be kept below 10 kOhm and the signal will be sampled at
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19 1000 Hz. Movement-related ERD and MVF-induced ERD will be evaluated in this
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22 study. For movement-related ERD, participants will be asked to perform finger taps
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25 three times (or attempt to move their finger if they cannot perform the movement
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28 fluently) on a computer keyboard with the index finger of their unaffected side, in
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31 response to auditory cues (i.e., a 300-ms beep sound) delivered at random intervals
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34 (from seven seconds to 10 seconds), and to relax their hand after the completion of the
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37 movement.
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43 For MVF-induced ERD, participants will be asked to perform finger taps three times
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46 on a computer keyboard with the index finger of their unaffected side, in response to
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49 auditory cues delivered at random intervals (from seven seconds to 10 seconds),⁴² and
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52 to relax their hand after the completion of the movement. A widely used EEG paradigm
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55 exploring the effects of MVF will be utilized in the present study;^{29 30 42-44} movements
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57
58 will be performed under two conditions. (1) MVF of the hand movement: Participants
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4 will be required to perform unilateral finger tapping while viewing MVF. MVF will be
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7 created using a physical mirror (406 × 432 mm) placed over their midsagittal plane,
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10 between both arms. (2) Direct visual feedback (DVF) of the hand movement:
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13 Participants will be required to perform unilateral finger tapping while directly looking
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15
16 at their moving finger. The affected hand will be hidden by a non-reflective board.
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22 The order of conditions will be allocated randomly by drawing lots. A total of 60
23
24
25 movements will be collected for each condition (affected index movement, unaffected
26
27
28 index with mirror view, and unaffected index with direct view), with 180 movements
29
30
31 in total.
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37 **EEG preprocessing**

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40 Raw EEG signals will be band-pass filtered between 1 and 80 Hz and then down-
41
42
43 sampled at 250 Hz. Additionally, a 50-Hz notch filter will be applied. Data will be
44
45
46 offline re-referenced to bilateral mastoid electrodes. Signals with significant movement
47
48
49 artifacts and long-term eye closure will be rejected during a visual inspection.
50
51
52 Subsequently, EEG will be segmented in 7000 ms epochs (pre-stimulus -3000 ms and
53
54
55 post-stimulus 4000 ms, with 0 as the first finger tap). Eye movement artifacts will be
56
57
58 corrected using an independent component analysis algorithm.⁴⁵ Typical components
59
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4 reflecting the eye blinks and horizontal movements will then be rejected.
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10 **EEG time-frequency analysis**

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12

13 Clean epochs will be analyzed in a time-frequency domain. The event-related spectral
14 perturbation (ERSP) method using the *newtimef* function of EEGLAB⁴⁶ will be used to
15
16 compute the ERD power. The ERD power will be baseline corrected. Subsequently, the
17
18 power will be averaged across all trials and converted to log power. Averaged ERD
19
20 powers at electrode sites C3 (ipsilesional hemisphere, IH) and C4 (contralesional
21
22 hemisphere, CH) will be extracted. Data from patients with right brain lesions will be
23
24 flipped to ensure that C3 channels stand for IHs and C4 channels stand for CHs.
25
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37 For movement-related ERD, the power at C3 will be used for further analysis. For
38
39 MVF-induced ERD, the powers at IH and CH during the movement phase will be
40
41 extracted and an asymmetric index will be calculated with the following formula:⁴⁷
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43
44
45
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48

$$49 \text{ Asymmetric index} = (\text{IH ERD power}) - (\text{CH ERD power})$$

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55 The difference of asymmetric indices under the mirror view and direct view will be
56
57 used to evaluate MVF-induced sensorimotor ERD^{42 43} and used in a further analysis.
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10 A more negative value indicates more activation toward the ipsilesional sensorimotor
11 area, during the mirror view condition, compared to the direct view condition. Mu-1 (8-
12 10 Hz), mu-2 (10-12 Hz), beta-1 (12-16 Hz), and beta-2 (16-30 Hz) will be investigated
13 separately.
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25 **Safety profile investigation**

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

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39
40 Statistical analysis will be performed using SPSS version 23.0. A mixed-effects model
41
42 with random intercepts and slopes will be used to detect any significant differences in
43 the rate of change in motor outcomes and sensorimotor ERD between the three groups,
44
45 because of its superiority in analyzing repeated measures data and dataset with missing
46
47 values. Group effects, time effects, and group-by-time interaction effects will be
48
49 included as fixed effects, and the random intercept and random slope of change in the
50
51 dependent variables over time will be included as random effects. Between-group
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4 differences will be investigated using the interaction effects. Maximum likelihood
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6
7 estimation will be chosen as the estimation method. The covariance structure is
8
9
10 assumed to be unstructured. For post-hoc comparisons, the level of significance will be
11
12
13 set at $p < 0.017$ after Bonferroni adjustment ($0.05/3$; $n = \text{number of comparisons}$), for
14
15
16 the comparison of interaction effects. Cohen's d will be calculated to determine the
17
18
19 effect size of the change scores for the behavioral motor outcomes between groups.
20
21
22 Immediate training effects (data from baseline to post-training) and the durability of
23
24
25 training effects (data from post-training to follow-up) will be separately investigated
26
27
28 with mixed-effect models. Frequency scores for each reported side effect and the
29
30
31 percentage of participants who pass the MCID of the FMA-UE and ARAT will be
32
33
34 compared using Chi-squared tests between the three groups.
35
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40 **Patient and public involvement**

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42
43 Patients will be invited to participate in this study via advertisements. Several self-help
44
45
46 stroke organizations will be notified in order to promote the enrollment. Patients will
47
48
49 not be involved in participant recruitment. The results of the evaluation can be released
50
51
52 to participants upon request.
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58 **Ethics and dissemination**

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4 This randomized controlled trial was registered on 24 July 2019
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7 (<https://clinicaltrials.gov>, see supplementary section for trial registration data). The
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10 study has launched on 9th September 2019 and will continue for around a year. The
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13 study will be conducted in accordance with the principles of the Declaration of Helsinki.
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16 Written informed consent forms will be collected from each participant before the study
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18
19 begins (see a template of written consent form in supplementary section). Ethical
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21
22 consideration has been sought from the human subject ethics subcommittee of the Hong
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24
25 Kong Polytechnic University. Any modifications to this study protocol will also be
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28 reviewed by the subcommittee. This study will only include participants who have
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30
31 given informed written consent and the confidentiality is assured. All original data will
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34 be kept in strictly private. During the study, written data will be stored in a safe place;
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37 after the study, all data will be input to a computer by the principle investigator and a
38
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40 backup of the data will be kept on a hard drive, which will be stored in a safe place.
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43 The input data will be double checked by another research assistant. Personal data will
44
45
46 be discarded after three years. Due to the small expected sample size of this proof-of-
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48
49 concept study, a data monitoring committee was not deemed to be required. We will
50
51
52 not perform interim analyses until the completion of this study. The results of this study
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54
55 will be presented at international conferences and sent to a peer-reviewed journal to be
56
57
58 considered for publication.
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10 **Authors' contributions:** JZ and KF were involved in the conception and design of the
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12 research. JZ wrote up the first draft of the research. KF reviewed and edited the
13
14 manuscript. JZ and KF approved the submission of the final version of the manuscript.
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21
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23
24 public, commercial, or not-for-profit sectors. Work of JZ was supported by PhD
25
26 studentships of The Hong Kong Polytechnic University.
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34 **Conflict of interests:** None declared
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40 **Patient consent for publication:** Not required.
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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.

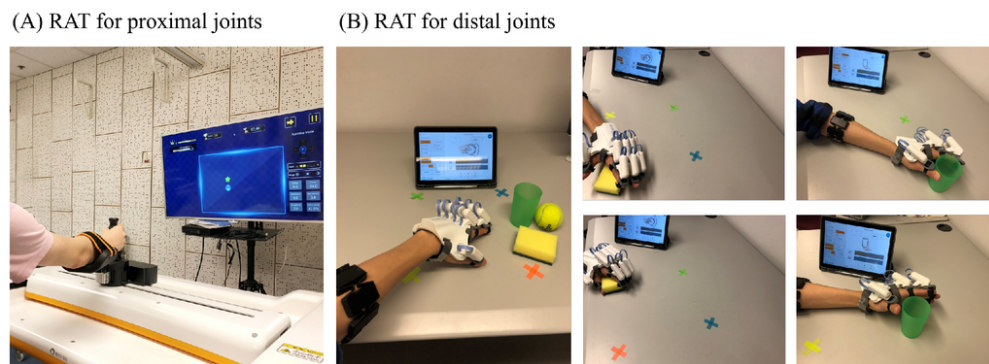
Figure 3. Schedule of participant recruitment, assessments, and intervention.

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.

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

21 87x32mm (300 x 300 DPI)

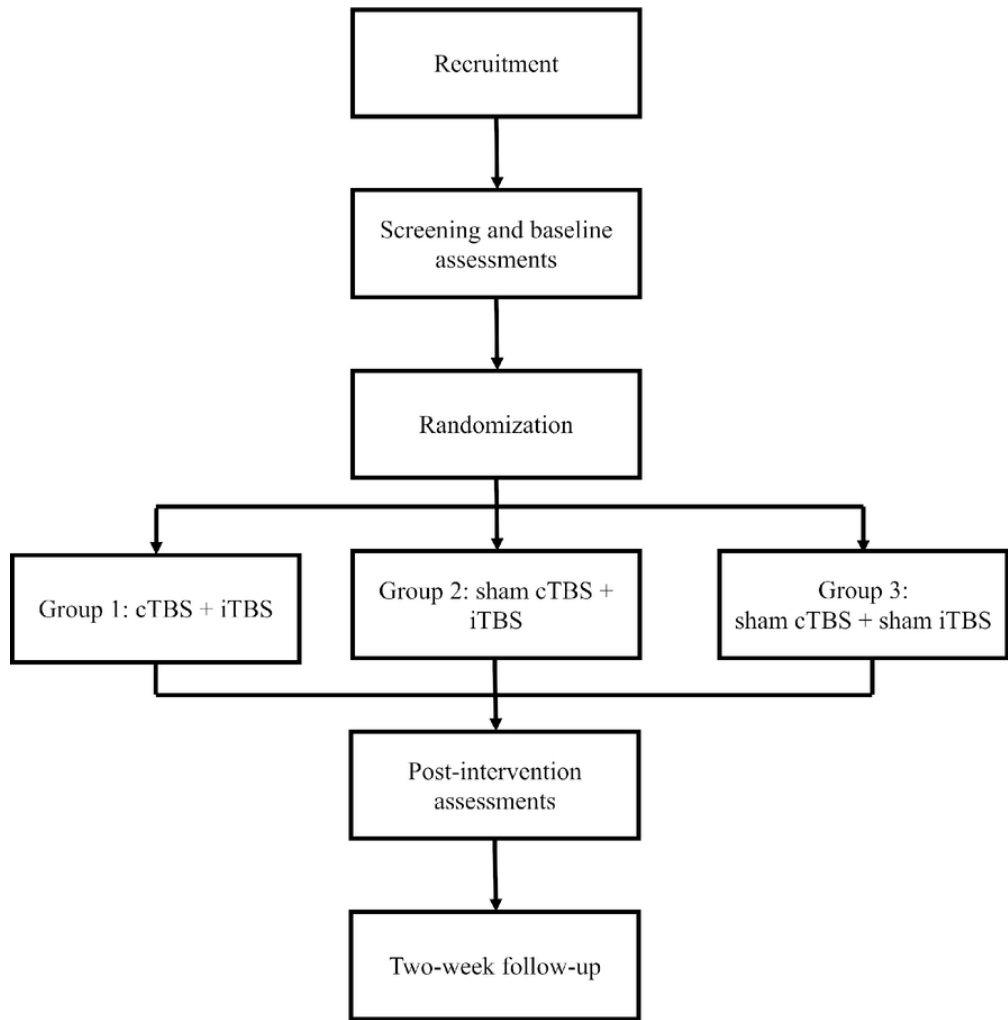


Figure 2. Flowchart of the proposed randomized controlled trial.

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.

72x70mm (300 x 300 DPI)

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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	2-5
Appendix: Template of written consent form	6-9

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)

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4 Abbreviations: cTBS: Continuous Theta Burst Stimulation; iTBS: Intermittent Theta

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7 Burst Stimulation; AMT: Abbreviated Mental Test; MAS: Modified Ashworth Scale;

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10 FMA-UE: Fugl-Meyer Assessment - Upper Extremity Scores; ARAT: Action Research

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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 SPIRIT reporting 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
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1	Trial registration	#2a	Trial identifier and registry name. If not yet	3
2			registered, name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	Supplementary
7	data set		Registration Data Set	section
8				
9				
10				
11				Table S1
12				
13				
14				
15	Protocol version	#3	Date and version identifier	Supplementary
16				section
17				
18				
19				
20				Table S1
21				
22				
23	Funding	#4	Sources and types of financial, material, and other	22
24			support	
25				
26				
27				
28				
29	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1; 22
30	responsibilities:			
31				
32	contributorship			
33				
34				
35				
36	Roles and	#5b	Name and contact information for the trial sponsor	Supplementary
37	responsibilities:			section
38				
39	sponsor contact			
40				
41				Table S1
42	information			
43				
44				
45				
46	Roles and	#5c	Role of study sponsor and funders, if any, in study	Supplementary
47	responsibilities:		design; collection, management, analysis, and	section
48				
49	sponsor and funder		interpretation of data; writing of the report; and the	
50				Table S1
51				
52				
53			decision to submit the report for publication, including	
54				
55			whether they will have ultimate authority over any of	
56				
57			these activities	
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1 Roles and [#5d](#) Composition, roles, and responsibilities of the NA
 2
 3 responsibilities:
 4 coordinating centre, steering committee, endpoint
 5 committees
 6 adjudication committee, data management team, and
 7
 8 other individuals or groups overseeing the trial, if
 9
 10 applicable (see Item 21a for data monitoring
 11
 12 committee)
 13
 14

15 Introduction

16
 17
 18 Background and [#6a](#) Description of research question and justification for 1-8
 19 rationale
 20 undertaking the trial, including summary of relevant
 21 studies (published and unpublished) examining
 22 benefits and harms for each intervention
 23
 24
 25
 26

27
 28 Background and [#6b](#) Explanation for choice of comparators 8
 29 rationale: choice of
 30 comparators
 31
 32
 33
 34
 35

36 Objectives [#7](#) Specific objectives or hypotheses 8
 37
 38

39 Trial design [#8](#) Description of trial design including type of trial (eg, 8
 40 parallel group, crossover, factorial, single group),
 41 allocation ratio, and framework (eg, superiority,
 42 equivalence, non-inferiority, exploratory)
 43
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49 Methods:

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 51 Participants,
 52 interventions, and
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 56 outcomes
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1	Study setting	#9	Description of study settings (eg, community clinic,	8-9
2			academic hospital) and list of countries where data	
3			will be collected. Reference to where list of study	
4			sites can be obtained	
5				
6				
7				
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10				
11	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	9-10
12			applicable, eligibility criteria for study centres and	
13			individuals who will perform the interventions (eg,	
14			surgeons, psychotherapists)	
15				
16				
17				
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20				
21	Interventions:	#11a	Interventions for each group with sufficient detail to	11-15
22			allow replication, including how and when they will be	
23	description		administered	
24				
25				
26				
27				
28				
29	Interventions:	#11b	Criteria for discontinuing or modifying allocated	11-15
30			interventions for a given trial participant (eg, drug	
31	modifications		dose change in response to harms, participant	
32			request, or improving / worsening disease)	
33				
34				
35				
36				
37				
38				
39	Interventions:	#11c	Strategies to improve adherence to intervention	11-15
40			protocols, and any procedures for monitoring	
41	adherence		adherence (eg, drug tablet return; laboratory tests)	
42				
43				
44				
45				
46	Interventions:	#11d	Relevant concomitant care and interventions that are	10
47			permitted or prohibited during the trial	
48	concomitant care			
49				
50				
51	Outcomes	#12	Primary, secondary, and other outcomes, including	15-20
52			the specific measurement variable (eg, systolic blood	
53			pressure), analysis metric (eg, change from baseline,	
54				
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1 final value, time to event), method of aggregation
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 3 (eg, median, proportion), and time point for each
 4
 5 outcome. Explanation of the clinical relevance of
 6
 7 chosen efficacy and harm outcomes is strongly
 8
 9 recommended
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 13 Participant timeline [#13](#) Time schedule of enrolment, interventions (including Figure 3
 14 any run-ins and washouts), assessments, and visits
 15 for participants. A schematic diagram is highly
 16 recommended (see Figure)
 17
 18
 19
 20

21
 22 Sample size [#14](#) Estimated number of participants needed to achieve 10-11
 23 study objectives and how it was determined,
 24 including clinical and statistical assumptions
 25 supporting any sample size calculations
 26
 27
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 32 Recruitment [#15](#) Strategies for achieving adequate participant 8-9
 33 enrolment to reach target sample size
 34
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38 Methods:

39 40 Assignment of 41 interventions (for 42 controlled trials)

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 47 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 11
 48 generation computer-generated random numbers), and list of
 49 any factors for stratification. To reduce predictability
 50 of a random sequence, details of any planned
 51 restriction (eg, blocking) should be provided in a
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1		separate document that is unavailable to those who	
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3		enrol participants or assign interventions	
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5			
6	Allocation	#16b Mechanism of implementing the allocation sequence	11
7			
8	concealment	(eg, central telephone; sequentially numbered,	
9			
10	mechanism	opaque, sealed envelopes), describing any steps to	
11		conceal the sequence until interventions are	
12			
13		assigned	
14			
15			
16			
17			
18	Allocation:	#16c Who will generate the allocation sequence, who will	11
19			
20	implementation	enrol participants, and who will assign participants to	
21		interventions	
22			
23			
24			
25	Blinding (masking)	#17a Who will be blinded after assignment to interventions	11-12
26			
27		(eg, trial participants, care providers, outcome	
28		assessors, data analysts), and how	
29			
30			
31			
32			
33	Blinding (masking):	#17b If blinded, circumstances under which unblinding is	NA
34			
35	emergency	permissible, and procedure for revealing a	
36			
37	unblinding	participant's allocated intervention during the trial	
38			
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41	Methods: Data		
42			
43	collection,		
44			
45	management, and		
46			
47	analysis		
48			
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50			
51	Data collection plan	#18a Plans for assessment and collection of outcome,	16
52			
53		baseline, and other trial data, including any related	
54			
55		processes to promote data quality (eg, duplicate	
56			
57		measurements, training of assessors) and a	
58			
59			
60			

1		description of study instruments (eg, questionnaires,	
2		laboratory tests) along with their reliability and	
3		validity, if known. Reference to where data collection	
4		forms can be found, if not in the protocol	
5			
6			
7			
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10	Data collection plan:	#18b Plans to promote participant retention and complete	16-17
11	retention	follow-up, including list of any outcome data to be	
12		collected for participants who discontinue or deviate	
13		from intervention protocols	
14			
15			
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19			
20	Data management	#19 Plans for data entry, coding, security, and storage,	21-22
21		including any related processes to promote data	
22		quality (eg, double data entry; range checks for data	
23		values). Reference to where details of data	
24		management procedures can be found, if not in the	
25		protocol	
26			
27			
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29			
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33			
34	Statistics: outcomes	#20a Statistical methods for analysing primary and	20
35		secondary outcomes. Reference to where other	
36		details of the statistical analysis plan can be found, if	
37		not in the protocol	
38			
39			
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42			
43			
44	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup	20
45	analyses	and adjusted analyses)	
46			
47			
48			
49			
50	Statistics: analysis	#20c Definition of analysis population relating to protocol	20
51	population and	non-adherence (eg, as randomised analysis), and	
52	missing data	any statistical methods to handle missing data (eg,	
53		multiple imputation)	
54			
55			
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1 **Methods: Monitoring**

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4 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); NA

5

6 formal committee

7 summary of its role and reporting structure;

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9 statement of whether it is independent from the

10

11 sponsor and competing interests; and reference to

12

13 where further details about its charter can be found, if

14

15

16 not in the protocol. Alternatively, an explanation of

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18 why a DMC is not needed

19

20

21 Data monitoring: [#21b](#) Description of any interim analyses and stopping NA

22

23 interim analysis

24 guidelines, including who will have access to these

25

26 interim results and make the final decision to

27

28 terminate the trial

29

30

31 Harms [#22](#) Plans for collecting, assessing, reporting, and NA

32

33 managing solicited and spontaneously reported

34

35 adverse events and other unintended effects of trial

36

37 interventions or trial conduct

38

39

40

41 Auditing [#23](#) Frequency and procedures for auditing trial conduct, NA

42

43 if any, and whether the process will be independent

44

45 from investigators and the sponsor

46

47

48 **Ethics and**

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50 **dissemination**

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54 Research ethics [#24](#) Plans for seeking research ethics committee / 21

55

56 approval

57 institutional review board (REC / IRB) approval

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1	Protocol	#25	Plans for communicating important protocol	21
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8				
9				
10				
11				
12				
13	Consent or assent	#26a	Who will obtain informed consent or assent from	21
14			potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18				
19				
20				
21	Consent or assent:	#26b	Additional consent provisions for collection and use	21
22	ancillary studies		of participant data and biological specimens in	
23			ancillary studies, if applicable	
24				
25				
26				
27				
28				
29	Confidentiality	#27	How personal information about potential and	21
30			enrolled participants will be collected, shared, and	
31			maintained in order to protect confidentiality before,	
32			during, and after the trial	
33				
34				
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38				
39	Declaration of	#28	Financial and other competing interests for principal	22
40	interests		investigators for the overall trial and each study site	
41				
42				
43				
44	Data access	#29	Statement of who will have access to the final trial	22
45			dataset, and disclosure of contractual agreements	
46			that limit such access for investigators	
47				
48				
49				
50				
51	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	NA
52	trial care		and for compensation to those who suffer harm from	
53			trial participation	
54				
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56				
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1	Dissemination	#31a	Plans for investigators and sponsor to communicate	21
2				
3	policy: trial results		trial results to participants, healthcare professionals,	
4			the public, and other relevant groups (eg, via	
5			publication, reporting in results databases, or other	
6			data sharing arrangements), including any	
7			publication restrictions	
8				
9				
10				
11				
12				
13				
14				
15	Dissemination	#31b	Authorship eligibility guidelines and any intended use	21
16				
17	policy: authorship		of professional writers	
18				
19				
20				
21	Dissemination	#31c	Plans, if any, for granting public access to the full	21
22				
23	policy: reproducible		protocol, participant-level dataset, and statistical	
24			code	
25	research			
26				
27				
28				
29	Appendices			
30				
31				
32	Informed consent	#32	Model consent form and other related documentation	Supplementary
33				
34	materials		given to participants and authorised surrogates	section
35				
36				
37				Table S1
38				
39				
40	Biological	#33	Plans for collection, laboratory evaluation, and	NA
41				
42	specimens		storage of biological specimens for genetic or	
43			molecular analysis in the current trial and for future	
44			use in ancillary studies, if applicable	
45				
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50 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
51 License CC-BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a
52 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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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.

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4 Secondary outcomes will be assessed using kinematic outcomes generated during RAT,
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7 and EEG.
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10 **Ethics and dissemination:** Ethical approval has been obtained from The Human
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13 Subjects Ethics Sub-committee, University Research Committee of The Hong Kong
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15
16 Polytechnic University (Reference number: HSEARS20190718003). The results
17
18
19 yielded from this study will be presented at international conferences and sent to a peer-
20
21
22 review journal to be considered for publication.
23
24

25 **Trial registration number:** NCT04034069.
26
27

28 **Keywords:** Theta burst stimulation; stroke; hemiparetic upper limb; priming;
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31 metaplasticity.
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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 potentiate 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.

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4 A substantial number of clinical trials with stroke patients have revealed that iTBS of
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7 the ipsilesional M1 significantly improves hemiplegic arm^{5 6 10-12} and hand⁸ motor
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9
10 functions, compared to sham stimulations. Similar effects have also been observed in
11
12
13 studies using cTBS of the contralesional M1.^{13 14} However, some trials have not shown
14
15
16 any additional benefits on upper limb motor outcomes from iTBS or cTBS in stroke
17
18
19 survivors, in contrast to sham TBS.^{7 13} A recent meta-analysis showed that a pooled
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21
22 standardized effect size of iTBS was 0.60, while that of cTBS was 0.35 for upper limb
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24
25 motor outcomes in patients with stroke,¹⁵ indicating that the increment of the
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27
28 excitability of the affected M1 through iTBS is critical for improving the brain's
29
30
31 response to motor training in patients with stroke. However, substantial response
32
33
34 variability regarding iTBS among humans may contribute to the use of different
35
36
37 protocols among current studies,^{16 17} which limits their clinical utility.

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42
43 It has been shown that the history of neuronal activities is one of the major factors that
44
45
46 could influence the brain's response to TBS.¹⁸ Synaptic plasticity is regulated by
47
48
49 previous neuronal activities via metaplasticity. Metaplasticity is a neuroprotective
50
51
52 mechanism that modulates the threshold of synaptic plasticity to ensure that the neural
53
54
55 system cannot be predominated by long-term potentiation (LTP) or long-term
56
57
58 depression (LTD).¹⁹ Excitatory rTMS over the M1 may be unable to facilitate
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4 corticomotor excitability when the neuronal activities have already been elevated
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6
7 before stimulation, which is likely happening when patients with stroke receive
8
9
10 extensive training before non-invasive brain stimulation.
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16 Considering the mechanism of metaplasticity, several priming stimulation protocols,
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18 designed to incorporate a priming session followed by a stimulation session, have been
19
20 investigated with healthy individuals.²⁰ An inhibitory priming stimulation via cTBS
21
22 may ensure or even boost the facilitatory effect of subsequent excitatory stimulation
23
24 sessions via iTBS. In healthy individuals, this priming protocol seems to amplify the
25
26 facilitatory effect of excitatory stimulation, compared with iTBS alone, as reflected by
27
28 the increased amplitude of motor evoked potential (MEP).²¹⁻²³ Metaplasticity is also
29
30 significantly involved in rTMS studies for patients with neuropsychiatric disorders.^{24 25}
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40 However, to date no study has investigated the effects of priming iTBS protocols in
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43 patients with stroke.
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49 Various neurological biomarkers of stroke motor recovery have been proposed.²⁶
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51
52 Electroencephalography (EEG), a non-invasive measure of cortical neuronal oscillation,
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54
55 is of great interest, because it is a relatively convenient and well-tolerated
56
57
58 neurophysiological technique for patients with stroke. Sensorimotor event-related
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4 desynchronization (ERD), a neurophysiological marker of sensorimotor activation,
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6
7 could be induced through either action observation or action execution.²⁷ Previously,
8
9
10 attention has been paid to movement-related sensorimotor ERD, which has been shown
11
12
13 to be correlated with the severity of hemiplegia in patients with stroke.^{28 29}
14
15
16 Subsequently, researchers began to investigate sensorimotor ERD induced by
17
18
19 observing mirror visual feedback (MVF) in healthy adults and patients with stroke.^{30 31}
20
21
22 A pilot study has demonstrated that multiple sessions of iTBS appear to enhance MVF-
23
24
25 induced sensorimotor ERD in healthy adults.³² So far, MVF-induced sensorimotor ERD
26
27
28 has not been used as an outcome of neuroplasticity in any clinical stroke trial in order
29
30
31 to examine its potential as a biomarker for stroke motor recovery. Sensorimotor ERD
32
33
34 will be used to probe cortical oscillatory activities of large number of neurons in
35
36
37 different rhythms, during a given task (movement or movement observation). A
38
39
40 previous study comparing the effects of TBS on MEPs and movement-related rhythmic
41
42
43 oscillations showed that the modulatory effect of TBS was more reliable on movement-
44
45
46 related ERD than that on MEPs.³³ The potential explanations may be that TMS-based
47
48
49 metrics may not represent all cortical responses, reflecting exclusively those destined
50
51
52 to the spinal cord,³³ and the magnitude of TMS-based metrics is also contaminated by
53
54
55 the neuronal responses at subcortical and spinal levels, as well as the peripheral MEP,³⁴
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57
58 when a suprathreshold stimulation intensity is used for the measurements. Hence, we
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4 decide to use sensorimotor desynchronization in this study, which may provide new
5
6
7 insight about the sensorimotor neuroplasticity in association with priming iTBS.
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13 Therefore, our study has two objectives. First, we investigate the effects of 10 sessions
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15
16 of rTMS using different TBS protocols (i.e., cTBS plus iTBS, sham cTBS plus iTBS,
17
18
19 and sham cTBS plus sham iTBS), in addition to standard robot-assisted training (RAT)
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21
22 for both the proximal and distal joints of the hemiparetic upper limb, delivered across
23
24
25 three to five sessions per week for two to three weeks, on improving the hemiparetic
26
27
28 upper limb functions of stroke survivors. Fugl-Meyer Assessment - Upper Extremity
29
30
31 (FMA-UE) scores and Action Research Arm Test (ARAT) will be used as the primary
32
33
34 outcome measures. Safety profiles will be systematically collected during each session
35
36
37 of the intervention, using a standard questionnaire. Second, we investigate the effects
38
39
40 of different TBS protocols, cTBS plus iTBS, sham cTBS plus iTBS, and sham cTBS
41
42
43 plus sham iTBS, in addition to RAT, on upper limb kinematic outcomes yielded from
44
45
46 each RAT session, and sensorimotor ERD induced by hemiparetic hand movement and
47
48
49 observation of the MVF of nonparetic hand movement, in patients with stroke.
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55 **Methods**

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58 This study protocol has been written according to the Standard Protocol Items for
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4 Randomized Trials statement.³⁵
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10 **Study design**

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12
13 This study is designed as a three-arm, parallel group, subjects- and assessors-blinded,
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15
16 sham-controlled RCT. Potential participants with stroke will be recruited through
17
18
19 convenience sampling from self-support groups in the community in Hong Kong. The
20
21
22 study will be conducted in a local university laboratory.
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28 **Inclusion and exclusion criteria**

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31 Participants must meet all of the following criteria: (1) have a diagnosis of a unilateral
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33
34 ischemic or hemorrhagic first-ever stroke; (2) time after stroke onset \geq 6 months;³⁶
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36
37 (3) between 18 and 64 years old; (4) reside in community dwellings; (4) with residual
38
39
40 upper limb impairment \geq second level in the Functional Test for the Hemiplegic
41
42
43 Upper Extremity (FTHUE).³⁷ FTHUE is a fast screening tool for upper limb functional
44
45
46 movement, which has been used as a screening in our previous RCTs.^{38 39} FTHUE
47
48
49 levels two to four are defined as low upper limb functioning poststroke, and levels five
50
51
52 and seven are defined as high upper limb functioning poststroke;³⁸ (5) able to
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55 understand simple verbal instruction and follow one-step commands; and (6) able to
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57
58 give informed written consent to participate in the study.
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7 Although TBS is often regarded as safe for certain subjects, the greatest acute risk of
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10 TMS is the rare occurrence of induced seizures. Besides seizures, other risks include
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13 minor pain, such as a headache or local discomfort, minor cognitive changes, and
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15
16 psychiatric symptoms. In this study, patients who meet any of the following rTMS
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19 contraindications will not be included: (1) unstable medical condition; (2) history of
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22 epileptic seizures, unconsciousness, or intracranial hypertension; (3) serious heart
23
24
25 disease; (4) pregnancy; (5) with metal implants *in vivo*, such as a pacemaker, artificial
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27
28 cochlear, or implant brain stimulator; (6) history of receiving a craniotomy; and (7)
29
30
31 taking any centrally acting drugs in the recent three months.² To ensure safety, the
32
33
34 participants will be under the supervision of at least one investigator who has completed
35
36
37 training in TMS. All participants will undergo a safety screening for the potential risks
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39
40 of TMS to ensure they are eligible to participate in this study.²
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46 In addition to TMS contraindications, participants who meet any of the following
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48
49 criteria will be also excluded: (1) previous diagnosis of any neurological disease
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51
52 excluding stroke; (2) presence of any sign of cognitive problems (Abbreviated Mental
53
54
55 Test, Hong Kong Cantonese version $< 6/10$);⁴⁰ (3) patients with extreme spasticity over
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57
58 the elbow or wrist in the hemiparetic upper limb (Modified Ashworth score > 2),⁴¹ or
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4 severe pain that hinders upper limb movement; (4) other notable impairments of the
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6
7 upper limb not affected by stroke (e.g., a recent fracture, severe osteoarthritis,
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10 congenital upper limb deformity); (5) significant aphasia or difficulty understanding
11
12
13 the instructions given by the investigators; (6) any sign of anxiety and/or depression
14
15
16 screened by the Hospital Anxiety and Depression Scale (HADS), using a cut-off value
17
18
19 of 8 in both subscales;⁴² and (7) concurrent participation in upper limb rehabilitation
20
21
22 training in a hospital, university laboratory or other rehabilitation settings, or active
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24
25 participation in another clinical trial.
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31 **Sample size estimation**

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34 Since the difference among the effects of priming iTBS in hemiparetic upper limb
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37 training has not been previously investigated, we have estimated the sample size based
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39
40 on current studies comparing iTBS and sham stimulation. A recent meta-analysis yields
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42
43 a pooled Cohen's *d* of 0.60 for a two-group design in favor of iTBS improving upper
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45
46 limb motor outcomes, in contrast to sham stimulation.¹⁵ An effect size (*d*) of 0.60
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48
49 corresponds approximately to an effect size (*f*) of 0.30 for a study design of three-group
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51
52 comparisons. An estimate of sample size for each group in a three-group design, given
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54
55 a power of 0.80 and a two-tailed alpha error probability of 0.05, is 27 patients in total.
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58 When considering the drop-out rate of 20%, we therefore plan to recruit 12 participants
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4 for each group (a total of 36) for this study.
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10 **Randomization**

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13 Three parallel groups will be employed: (1) cTBS plus iTBS; (2) sham cTBS plus iTBS;
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15 and (3) sham cTBS plus sham iTBS. The collection of demographic characteristics (age,
16
17 gender, education, side of hemiplegia, handedness, type of stroke, time from onset to
18
19 treatment, lesion site(s)) and baseline assessments will be performed prior to
20
21 randomization. Participants' medical information related to their stroke will be
22
23 retrieved from the electronic clinical management system in the hospital after receiving
24
25 consent. All participants will be randomly allocated in a 1:1:1 ratio to each group after
26
27 the screening and baseline assessments have been carried out. A random sequence will
28
29 be generated using Minimize software.⁴³ Participants will be pre-stratified based on
30
31 their hemiparetic upper limb functioning (i.e., FTHUE high functioning vs. low
32
33 functioning). The allocation sequence will be concealed from all investigators and
34
35 assessors. Participants will receive 10 sessions of TBS intervention combined with
36
37 RAT, 3 to 5 sessions per week, for two to three weeks. We decide to adopt a more
38
39 flexible training schedule, because most community stroke survivors are unable to visit
40
41 our laboratory on a daily basis. Similar schedule for motor training has been used in
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43 previous studies for patients with chronic stroke.^{44 45}
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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

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4 session and the conditioning session will be 10 minutes.^{21 25} All participants will be
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6
7 informed that TBS is delivered in a subthreshold intensity that cannot induce significant
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10 limb movement or somatosensory perception.
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16 **Robot-assisted training**

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19 Participants will be required to undergo two forms of RAT for the proximal and distal
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21 joints of the hemiparetic upper limb, respectively, after each TBS session. RAT will
22
23 commence five minutes after the completion of the TBS session.¹¹ A Fourier M2 robot
24
25 (Fourier Intelligence Company Limited., Shanghai, China) will be used for the upper
26
27 limb proximal joint training. The Fourier M2 robot is an end-effector robot-assisted
28
29 upper limb rehabilitation device, supported by tailored interactive television games in
30
31 the device. A HandyRehab hand robot (Zunosaki Company Limited., Hong Kong SAR,
32
33 China) will be used for upper limb distal joint training. The device provides power-
34
35 driven extension and grasping force to the fingers and thumb in order to assist the
36
37 patient with opening and closing the paretic hand by means of surface
38
39 electromyography (EMG) triggered from the signals through the forearm extensors and
40
41 flexors. Active and passive modes are available in both robots. Whenever patients are
42
43 unable to use the active modes due to the severity of the upper limb hemiplegia, passive
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45 modes will be used.
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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

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4 robot with a computer screen attached to the device. The participant will wear a trunk-
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7 fixed belt to minimize compensatory movement of the trunk during training.
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10 11 12 13 **Distal joint training** 14

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16 The HandyRehab hand robot is lightweight, powered by lithium batteries, and allows
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18 the subject to perform a full hand grasp/release movement in either the spherical grip
19
20 or cylindrical grip mode. The EMG trigger threshold will be adjusted based on patients'
21
22 hemiplegic arm function. Participants will be instructed to perform the different types
23
24 of hand movements to pick up an object (i.e., a ball, sponge, or a cup) on a table, move
25
26 it vertically and/or horizontally to four predefined targets, and release the object. The
27
28 distance between the targets and participants will be adjusted based on their active
29
30 ROM of proximal joints in the paretic upper limb. The EMG-triggered level will be
31
32 adjusted based on patients' ability (i.e., active mode) and gradually increased as the
33
34 training progresses. For patients without any detectable EMG signal from the paretic
35
36 forearm, the passive mode will be used. Each distal joint training session will last for
37
38 around 30 minutes, with a break of five to 10 minutes (see Figure 1B for a
39
40 demonstration of distal joint RAT). In total, each RAT session lasts for approximately
41
42 60 minutes (30 minutes for proximal joints and 30 minutes for distal joints), with 10
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44 sessions in total. An investigator with a background in physiotherapy or occupational
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4 therapy will supervise each participant during each robot training session to ensure the
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7 correct positioning is used and that participants become familiar with the training.
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10 11 12 13 **Outcome measurements**

14 15 16 **Primary outcomes**

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19 The FMA-UE and ARAT will be used as the primary outcomes for this study.⁴⁷ The

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21
22 FMA-UE is a clinical assessment for upper limb motor impairment after stroke. It
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24
25 includes 33 items assessing the movement, coordination, and reflex actions of the
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27
28 shoulder, elbow, forearm, and wrist, and the hand joints of the paretic arm. Each item
29
30
31 consists of a three-point scale (zero, one, and two), with a total maximum score of 66.

32
33
34 The minimal clinically important difference (MCID) of the FMA-UE is 5.25 points.⁴⁸

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36
37 The FMA-UE will be conducted at four time points: baseline, mid-term (i.e., after five
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39
40 sessions), post-training (i.e., after 10 sessions), and follow-up (i.e., two weeks after the
41
42
43 completion of all training sessions). An assessor who is unaware of the treatment
44
45
46 allocation will carry out the assessment for each participant. The ARAT is a clinical
47
48
49 assessment for upper limb functional activities for patients with stroke. The ARAT
50
51
52 assesses proximal and distal components of upper limb function. It consists of four
53
54
55 subscales: grasp, grip, pinch, and gross movement. It has 19 movement tasks, each
56
57
58 graded using a four-point scale (total scores range from 0 to 57). The MCID of ARAT
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4 is 5.70 points.⁴⁹ ARAT will be conducted at the same four time points as the FMA-UE.
5
6

7 An assessor who is unaware of the treatment allocation will carry out the assessment
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9
10 for each participant. Assessors will be trained and tested by the principle investigator,
11
12
13 before conducting clinical assessments.
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18 19 **Secondary outcomes**

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21 Kinematic metrics generated during each session of RAT will be used as secondary
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23 outcomes for the participants' upper limb function. The following kinematic metrics
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25 retrieved from the M2 robot will be used as the upper limb motor outcomes in a further
26
27 analysis: (1) the size of the maximal active ROM; (2) the mean velocity of movement
28
29 during the training session; and (3) the movement trajectory during the training session.
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31
32 Movement trajectory will be further calculated as the hand-path ratio, which is defined
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34 as the real distance divided by the shortest distance between object targets.⁵⁰
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46 In order to investigate the potential neuroplasticity elicited by the training, we will
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48 invite patients to participate in EEG examinations. We expect that around five patients
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50 from each group will take part in the EEG examinations before and after the
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52 intervention. Kinematic and EEG outcomes will be assessed in a non-blinded manner
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55
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57
58 (see Figure 2 for a flowchart).
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60

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

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4 created using a physical mirror (406 × 432 mm) placed over their midsagittal plane,
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7 between both arms. (2) Direct visual feedback (DVF) of the hand movement:
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10 Participants will be required to perform unilateral finger tapping while directly looking
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13 at their moving finger. The affected hand will be hidden by a non-reflective board.
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19 The order of conditions will be allocated randomly by drawing lots. A total of 60
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22 movements will be collected for each condition (affected index movement, unaffected
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24
25 index with mirror view, and unaffected index with direct view), with 180 movements
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28 in total.
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34 **EEG preprocessing**

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37 Raw EEG signals will be band-pass filtered between 1 and 80 Hz and then down-
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40 sampled at 250 Hz. Additionally, a 50-Hz notch filter will be applied. Data will be
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43 offline re-referenced to bilateral mastoid electrodes. Signals with significant movement
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46 artifacts and long-term eye closure will be rejected during a visual inspection.
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49 Subsequently, EEG will be segmented in 7000 ms epochs (pre-stimulus -3000 ms and
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52 post-stimulus 4000 ms, with 0 as the first finger tap). Eye movement artifacts will be
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55 corrected using an independent component analysis algorithm.⁵³ Typical components
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57
58 reflecting the eye blinks and horizontal movements will then be rejected.
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60

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 EEGLAB⁵⁴ 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,

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4 during the mirror view condition, compared to the direct view condition. Mu-1 (8-10
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7 Hz), mu-2 (10-12 Hz), beta-1 (12-16 Hz), and beta-2 (16-30 Hz) will be investigated
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10 separately.³²
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16 **Safety profile investigation**

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

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31 Statistical analysis will be performed using SPSS version 23.0. Demographic and
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34 baseline characteristics will be compared using analysis of variance (ANOVA;
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37 continuous and ordinal data) or Chi-square tests (categorical data). A mixed-effects
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40 model with random intercepts and slopes will be used to detect any significant
41
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43 differences in the rate of change in motor outcomes and sensorimotor ERD among the
44
45
46 three groups, because of its superiority in analyzing repeated measures data and dataset
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48
49 with missing values. Any factor with significant between-group difference in the
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51
52 baseline will be included in the mixed-effects model as covariates. Group effects, time
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54
55 effects, and group-by-time interaction effects will be included as fixed effects, and the
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57
58 random intercept and random slope of change in the dependent variables over time will
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4 be included as random effects. Between-group differences will be investigated using
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6
7 the interaction effects. Maximum likelihood estimation will be chosen as the estimation
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9
10 method. The covariance structure is assumed to be unstructured. The level of
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12
13 significance will be set at $p < 0.05$. For post-hoc comparisons, the level of significance
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15
16 will be set at $p < 0.017$ after Bonferroni adjustment ($0.05/3$; $n =$ number of comparisons),
17
18
19 for the comparison of interaction effects. Cohen's d will be calculated to determine the
20
21
22 effect size of the change scores for the behavioral motor outcomes between groups.
23
24
25 Immediate training effects (data from baseline to post-training) and the durability of
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28 training effects (data from post-training to follow-up) will be separately investigated
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31 with mixed-effect models. Frequency scores for each reported side effect and the
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34 percentage of participants who pass the MCID of the FMA-UE and ARAT will be
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37 compared using Chi-squared tests between the three groups.
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43 **Patient and public involvement**

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

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4 This randomized controlled trial was registered on 24 July 2019
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7 (<https://clinicaltrials.gov>, see supplementary section for trial registration data). The
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10 study has launched on 9th September 2019 and will continue for around a year. The
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13 study will be conducted in accordance with the principles of the Declaration of Helsinki.
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16 Written informed consent forms will be collected from each participant before the study
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19 begins (see a template of written consent form in supplementary section). Ethical
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22 consideration has been approved from the human subject ethics subcommittee of the
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25 Hong Kong Polytechnic University. Any modifications to this study protocol will also
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28 be reviewed by the subcommittee. This study will only include participants who have
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31 given informed written consent and the confidentiality is assured. All original data will
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34 be kept in strictly private. During the study, written data will be stored in a safe place;
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37 after the study, all data will be input to a computer by the principle investigator and a
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40 backup of the data will be kept on a hard drive, which will be stored in a safe place.
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43 The input data will be double checked by another research assistant. Personal data will
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46 be discarded after three years. Due to the small expected sample size of this proof-of-
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49 concept study, a data monitoring committee was not deemed to be required and we will
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52 perform interim analyses when 50% of patients have been included and have completed
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55 the follow-up assessment. . The results of this study will be presented at international
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58 conferences and sent to a peer-reviewed journal to be considered for publication.
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7 **Authors' contributions:** JZ and KF were involved in the conception and design of the
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10 research. JZ wrote up the first draft of the research. KF reviewed and edited the
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13 manuscript. JZ and KF approved the submission of the final version of the manuscript.
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18
19 **Funding:** This research receives no specific grant from any funding agency in the
20
21
22 public, commercial, or not-for-profit sectors. Work of JZ was supported by PhD
23
24
25 studentships of The Hong Kong Polytechnic University.
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31 **Conflict of interests:** None declared
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37 **Patient consent for publication:** Not required.
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46 Jack Jiaqi ZHANG: 0000-0002-4656-1909
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49 Kenneth N.K. FONG: 0000-0001-5909-4847
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52 53 54 **References**

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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.

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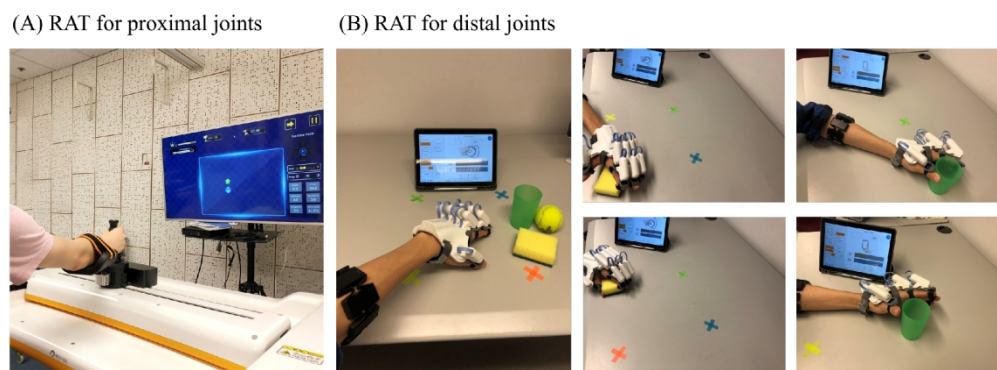
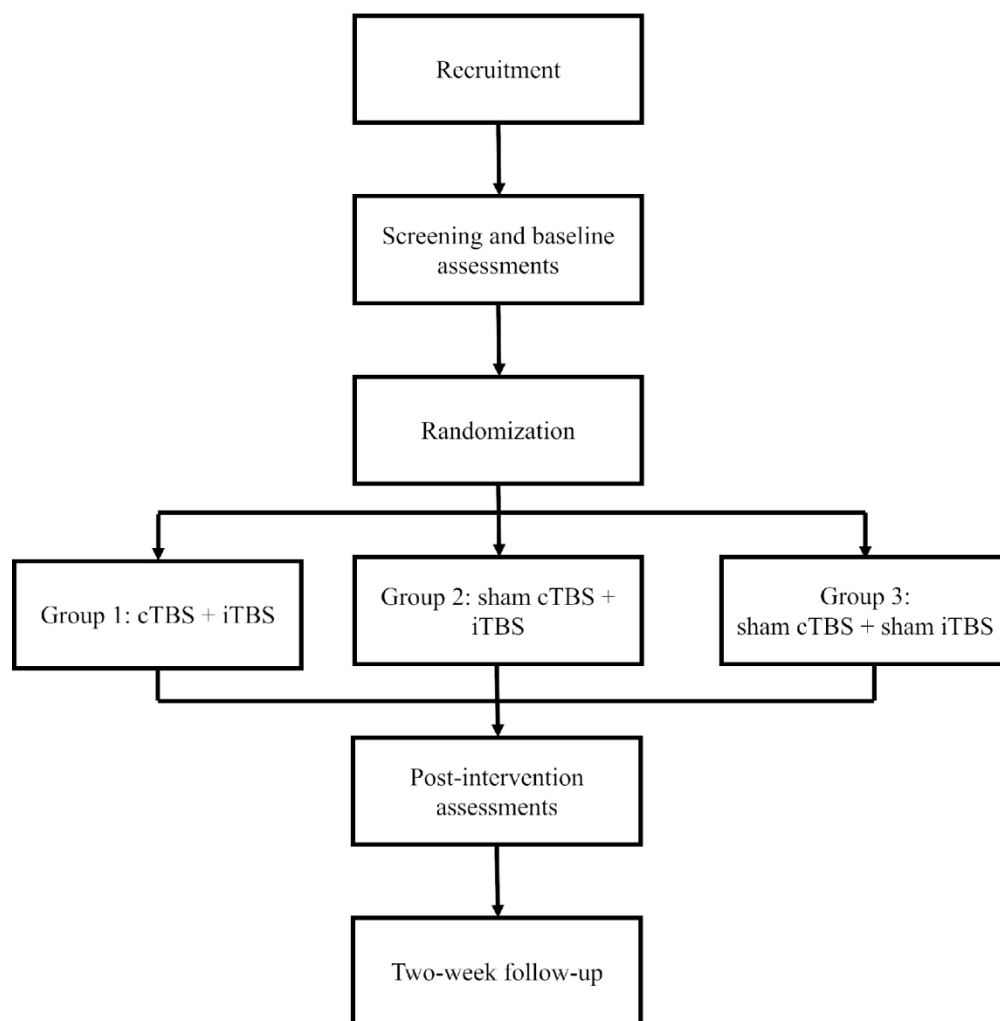


Figure 1. A demonstration of RAT. *Note The persons depicted are not patient and were taken with the participants knowledge.



39 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.

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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 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	2-5
Appendix: Template of written consent form	6-9

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

	<p>months after stroke onset), with upper limb impairment (FTUHK from 2 to 7).</p> <p>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)</p>
Study type	<p>Interventional</p> <p>Allocation: randomized intervention model.</p> <p>Parallel assignment masking: single-blinded (outcomes assessor)</p> <p>Primary purpose: intervention</p>
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)

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4 Abbreviations: cTBS: Continuous Theta Burst Stimulation; iTBS: Intermittent Theta

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7 Burst Stimulation; AMT: Abbreviated Mental Test; MAS: Modified Ashworth Scale;

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10 FMA-UE: Fugl-Meyer Assessment - Upper Extremity Scores; ARAT: Action Research

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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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet	3
2			registered, name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	Supplementary
7	data set		Registration Data Set	section
8				
9				
10				
11				Table S1
12				
13				
14				
15	Protocol version	#3	Date and version identifier	Supplementary
16				section
17				
18				
19				
20				Table S1
21				
22				
23	Funding	#4	Sources and types of financial, material, and other	26
24			support	
25				
26				
27				
28				
29	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1; 26
30	responsibilities:			
31				
32	contributorship			
33				
34				
35				
36	Roles and	#5b	Name and contact information for the trial sponsor	Supplementary
37	responsibilities:			section
38				
39	sponsor contact			
40				
41				Table S1
42	information			
43				
44				
45				
46	Roles and	#5c	Role of study sponsor and funders, if any, in study	Supplementary
47	responsibilities:		design; collection, management, analysis, and	section
48				
49	sponsor and funder		interpretation of data; writing of the report; and the	
50				Table S1
51				
52				
53			decision to submit the report for publication, including	
54				
55			whether they will have ultimate authority over any of	
56				
57			these activities	
58				
59				
60				

1	Roles and	#5d	Composition, roles, and responsibilities of the	NA
2				
3	responsibilities:		coordinating centre, steering committee, endpoint	
4				
5	committees		adjudication committee, data management team, and	
6				
7			other individuals or groups overseeing the trial, if	
8				
9			applicable (see Item 21a for data monitoring	
10				
11			committee)	
12				
13				
14				
15	Introduction			
16				
17				
18				
19	Background and	#6a	Description of research question and justification for	1-9
20				
21	rationale		undertaking the trial, including summary of relevant	
22				
23			studies (published and unpublished) examining	
24				
25			benefits and harms for each intervention	
26				
27				
28				
29	Background and	#6b	Explanation for choice of comparators	9
30				
31	rationale: choice of			
32				
33	comparators			
34				
35				
36	Objectives	#7	Specific objectives or hypotheses	9
37				
38				
39	Trial design	#8	Description of trial design including type of trial (eg,	9-10
40				
41			parallel group, crossover, factorial, single group),	
42				
43			allocation ratio, and framework (eg, superiority,	
44				
45			equivalence, non-inferiority, exploratory)	
46				
47				
48				
49	Methods:			
50				
51	Participants,			
52				
53	interventions, and			
54				
55	outcomes			
56				
57				
58				
59				
60				

1	Study setting	#9	Description of study settings (eg, community clinic,	10
2			academic hospital) and list of countries where data	
3			will be collected. Reference to where list of study	
4			sites can be obtained	
5				
6				
7				
8				
9				
10				
11	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	10-11
12			applicable, eligibility criteria for study centres and	
13			individuals who will perform the interventions (eg,	
14			surgeons, psychotherapists)	
15				
16				
17				
18				
19				
20				
21	Interventions:	#11a	Interventions for each group with sufficient detail to	14-18
22			allow replication, including how and when they will be	
23	description		administered	
24				
25				
26				
27				
28				
29	Interventions:	#11b	Criteria for discontinuing or modifying allocated	14-18
30			interventions for a given trial participant (eg, drug	
31	modifications		dose change in response to harms, participant	
32			request, or improving / worsening disease)	
33				
34				
35				
36				
37				
38				
39	Interventions:	#11c	Strategies to improve adherence to intervention	14-18
40			protocols, and any procedures for monitoring	
41	adherence		adherence (eg, drug tablet return; laboratory tests)	
42				
43				
44				
45				
46	Interventions:	#11d	Relevant concomitant care and interventions that are	14-18
47			permitted or prohibited during the trial	
48	concomitant care			
49				
50				
51	Outcomes	#12	Primary, secondary, and other outcomes, including	18-19
52			the specific measurement variable (eg, systolic blood	
53			pressure), analysis metric (eg, change from baseline,	
54				
55				
56				
57				
58				
59				
60				

1 final value, time to event), method of aggregation
 2
 3 (eg, median, proportion), and time point for each
 4
 5 outcome. Explanation of the clinical relevance of
 6
 7 chosen efficacy and harm outcomes is strongly
 8
 9 recommended
 10

11
 12
 13 Participant timeline [#13](#) Time schedule of enrolment, interventions (including Figure 3
 14
 15 any run-ins and washouts), assessments, and visits
 16
 17 for participants. A schematic diagram is highly
 18
 19 recommended (see Figure)
 20

21
 22 Sample size [#14](#) Estimated number of participants needed to achieve 10-11
 23
 24 study objectives and how it was determined,
 25
 26 including clinical and statistical assumptions
 27
 28 supporting any sample size calculations
 29
 30

31
 32 Recruitment [#15](#) Strategies for achieving adequate participant 24
 33
 34 enrolment to reach target sample size
 35
 36

37 Methods:

38 Assignment of 39 40 interventions (for 41 42 controlled trials) 43 44

45
 46
 47 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 13
 48
 49 generation computer-generated random numbers), and list of
 50
 51 any factors for stratification. To reduce predictability
 52
 53 of a random sequence, details of any planned
 54
 55 restriction (eg, blocking) should be provided in a
 56
 57
 58
 59
 60

1		separate document that is unavailable to those who	
2			
3		enrol participants or assign interventions	
4			
5			
6	Allocation	#16b Mechanism of implementing the allocation sequence	13
7			
8	concealment	(eg, central telephone; sequentially numbered,	
9			
10	mechanism	opaque, sealed envelopes), describing any steps to	
11		conceal the sequence until interventions are	
12			
13		assigned	
14			
15			
16			
17			
18	Allocation:	#16c Who will generate the allocation sequence, who will	13
19			
20	implementation	enrol participants, and who will assign participants to	
21		interventions	
22			
23			
24			
25	Blinding (masking)	#17a Who will be blinded after assignment to interventions	14-15;
26			
27		(eg, trial participants, care providers, outcome	
28			18-19
29		assessors, data analysts), and how	
30			
31			
32			
33	Blinding (masking):	#17b If blinded, circumstances under which unblinding is	NA
34			
35	emergency	permissible, and procedure for revealing a	
36			
37	unblinding	participant's allocated intervention during the trial	
38			
39			
40			
41	Methods: Data		
42			
43	collection,		
44			
45	management, and		
46			
47	analysis		
48			
49			
50			
51	Data collection plan	#18a Plans for assessment and collection of outcome,	18-19
52			
53		baseline, and other trial data, including any related	
54			
55		processes to promote data quality (eg, duplicate	
56			
57		measurements, training of assessors) and a	
58			
59			
60			

1		description of study instruments (eg, questionnaires,	
2		laboratory tests) along with their reliability and	
3		validity, if known. Reference to where data collection	
4		forms can be found, if not in the protocol	
5			
6			
7			
8			
9			
10	Data collection plan:	#18b Plans to promote participant retention and complete	24
11	retention	follow-up, including list of any outcome data to be	
12		collected for participants who discontinue or deviate	
13		from intervention protocols	
14			
15			
16			
17			
18			
19			
20	Data management	#19 Plans for data entry, coding, security, and storage,	24-25
21		including any related processes to promote data	
22		quality (eg, double data entry; range checks for data	
23		values). Reference to where details of data	
24		management procedures can be found, if not in the	
25		protocol	
26			
27			
28			
29			
30			
31			
32			
33			
34	Statistics: outcomes	#20a Statistical methods for analysing primary and	23-24
35		secondary outcomes. Reference to where other	
36		details of the statistical analysis plan can be found, if	
37		not in the protocol	
38			
39			
40			
41			
42			
43			
44	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup	23-24
45	analyses	and adjusted analyses)	
46			
47			
48			
49			
50	Statistics: analysis	#20c Definition of analysis population relating to protocol	23-24
51	population and	non-adherence (eg, as randomised analysis), and	
52	missing data	any statistical methods to handle missing data (eg,	
53		multiple imputation)	
54			
55			
56			
57			
58			
59			
60			

1 **Methods: Monitoring**

2

3

4 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); NA

5

6 formal committee

7 summary of its role and reporting structure;

8

9 statement of whether it is independent from the

10

11 sponsor and competing interests; and reference to

12

13 where further details about its charter can be found, if

14

15

16 not in the protocol. Alternatively, an explanation of

17

18 why a DMC is not needed

19

20

21 Data monitoring: [#21b](#) Description of any interim analyses and stopping NA

22

23 interim analysis

24 guidelines, including who will have access to these

25

26 interim results and make the final decision to

27

28 terminate the trial

29

30

31 Harms [#22](#) Plans for collecting, assessing, reporting, and NA

32

33 managing solicited and spontaneously reported

34

35 adverse events and other unintended effects of trial

36

37 interventions or trial conduct

38

39

40

41 Auditing [#23](#) Frequency and procedures for auditing trial conduct, NA

42

43 if any, and whether the process will be independent

44

45 from investigators and the sponsor

46

47

48 **Ethics and**

49

50 **dissemination**

51

52

53

54 Research ethics [#24](#) Plans for seeking research ethics committee / 24-25

55

56 approval

57 institutional review board (REC / IRB) approval

58

59

60

1	Protocol	#25	Plans for communicating important protocol	24-25
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
8				
9				
10				
11				
12				
13	Consent or assent	#26a	Who will obtain informed consent or assent from	24-25
14			potential trial participants or authorised surrogates,	
15			and how (see Item 32)	
16				
17				
18				
19				
20				
21	Consent or assent:	#26b	Additional consent provisions for collection and use	24-25
22	ancillary studies		of participant data and biological specimens in	
23			ancillary studies, if applicable	
24				
25				
26				
27				
28				
29	Confidentiality	#27	How personal information about potential and	24-25
30			enrolled participants will be collected, shared, and	
31			maintained in order to protect confidentiality before,	
32			during, and after the trial	
33				
34				
35				
36				
37				
38				
39	Declaration of	#28	Financial and other competing interests for principal	26
40	interests		investigators for the overall trial and each study site	
41				
42				
43				
44	Data access	#29	Statement of who will have access to the final trial	24-25
45			dataset, and disclosure of contractual agreements	
46			that limit such access for investigators	
47				
48				
49				
50				
51	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	NA
52	trial care		and for compensation to those who suffer harm from	
53			trial participation	
54				
55				
56				
57				
58				
59				
60				

1	Dissemination	#31a	Plans for investigators and sponsor to communicate	24-25
2				
3	policy: trial results		trial results to participants, healthcare professionals,	
4			the public, and other relevant groups (eg, via	
5			publication, reporting in results databases, or other	
6			data sharing arrangements), including any	
7			publication restrictions	
8				
9				
10				
11				
12				
13				
14				
15	Dissemination	#31b	Authorship eligibility guidelines and any intended use	24-26
16				
17	policy: authorship		of professional writers	
18				
19				
20				
21	Dissemination	#31c	Plans, if any, for granting public access to the full	24-25
22				
23	policy: reproducible		protocol, participant-level dataset, and statistical	
24			code	
25	research			
26				
27				
28				
29	Appendices			
30				
31				
32	Informed consent	#32	Model consent form and other related documentation	Supplementary
33				
34	materials		given to participants and authorised surrogates	section
35				
36				
37				Table S1
38				
39				
40	Biological	#33	Plans for collection, laboratory evaluation, and	NA
41				
42	specimens		storage of biological specimens for genetic or	
43			molecular analysis in the current trial and for future	
44			use in ancillary studies, if applicable	
45				
46				
47				
48				
49				

50 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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 52 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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