Augmented efficacy of intermittent theta burst stimulation on the virtual reality-based cycling training for upper limb function in patients with stroke: a double-blinded, randomized controlled trial

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Keywords: Theta burst stimulation, Virtual reality, Stroke, Upper limb, Motor function, Rehabilitation

Posted Date: February 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-75545/v2

Abstract

Background: Virtual reality and arm cycling have been reported as effective treatment to improve upper limb motor recovery in patients with stroke. Intermittent theta burst stimulation (iTBS) can increase ipsilesional cortical excitability, and has been increasingly used in patients with stroke. However, few studies examined the augmented effect of iTBS on neurorehabilitation program. In this study, we investigated the augmented effect of iTBS on virtual reality-based cycling training (VCT) for upper limb motor function in patients with stroke.

Methods: In this randomized controlled trial, 23 patients with stroke were recruited. Each patient received either 15 sessions of iTBS or sham stimulation in addition to VCT on the same day. Outcome measures were assessed before and after the intervention. Co-primary outcome measures for body function were Modified Ashworth Scale Upper Extremity (MAS-UE) and Fugl-Meyer Assessment Upper Extremity (FMA-UE). Secondary outcome measures for activity and participation were Action Research Arm Test (ARAT), Nine Hole Peg Test (NHPT), Box and Block Test (BBT) and Motor Activity Log (MAL), and Stroke Impact Scale (SIS). Paired *t* test was performed to evaluate the effectiveness after the intervention and analysis of covariance (ANCOVA) was conducted to compare the therapeutic effects between two groups.

Results: At post-treatment, both groups showed significant improvement in FMA-UE and ARAT, while only the iTBS group demonstrated significant improvement in MAS-UE, BBT, NHPT, MAL and SIS. ANCOVA revealed that the iTBS group presented greater improvement than the sham group significantly in MAS-UE, NHPT and SIS. However, there were no significant differences in the changes of the FMA-UE, ARAT, BBT, and MAL between groups.

Conclusions: Intermittent TBS showed augmented efficacy on VCT for reducing spasticity, improving manual dexterity, and increasing participation in daily life in stroke patients. This study provided an integrated innovative intervention, which may be a promising therapy to improve upper limb motor function recovery, especially manual dexterity, in stroke rehabilitation. However, this study has a small sample size, and thus a further larger-scale study is warranted to confirm the treatment efficacy.

Trial registration: This trial was registered under ClinicalTrials.gov ID No. NCT03350087, retrospectively registered, on November 22, 2017.

Background

Stroke is a leading cause of upper limb (UL) motor impairments. UL impairment commonly persists after the acute phase [1], resulting in long-term disability and decreased health-related life quality. Despite receiving traditional neurorehabilitation programs, 50-60% of post-stroke patients remained functional motor limitations at variable degrees [2]. Various interventions and rehabilitation protocols have been developed in recent decades to enhance motor recovery and improve the quality of life in post-stroke patients. These rehabilitation programs include constraint-induced movement therapy, mirror therapy, and virtual reality (VR). Interventions include non-invasive brain stimulation (NIBS) and laser therapy.

Holden et al identified repetition, positive feedback and patient's motivation as the three key elements for post-stroke patients to achieve optimal functional recovery [3]. Therefore, this study combines VR with arm cycling to attain those elements. With the advancement of technology, VR has been increasingly utilized to treat neurological disorders. VR provides real-time somatosensory feedback to enhance motor control and learning [4], and initiates motivation for patients to endure repeated practice. Additionally, arm cycling was selected for the current rehabilitation program because it involves repetitive movement of bilateral upper limbs. Previous studies have demonstrated that bilateral extremities training induces interhemispheric facilitation [5], and that a repetitive training program provides additional benefit for functional recovery of upper limbs [6, 7]. A randomized controlled trial with 21 chronic patients found that bilateral arm training with rhythmic auditory cueing (BATRAC), a repetitive bilateral training therapy, induces reorganization in bilateral hemispheres [8]. Furthermore, unilateral virtual reality-based cycling training (VCT) was difficult for patients with hemiplegia. Taken together, this study applied bilateral VCT program for UL rehabilitation.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, has been increasingly reported as a promising intervention to safely improve motor performance in the affected UL of stroke patients. Although the precise underlying mechanism remains unclear, rTMS is generally considered to improve functional outcome in patients with stroke by modulating motor cortical excitability and inducing reorganization of neural networks [9]. Intermittent theta burst stimulation (iTBS) is a variant of rTMS that may provide equivalent or even better efficacy. Therefore, this study explores the augmented efficacy provided by iTBS on the neurorehabilitation program to improve UL motor function.

Theta burst stimulation (TBS) is a novel stimulation protocol of rTMS that requires a lower stimulation intensity within a shorter time to achieve therapeutic effect in post-stroke patients [10]. Previous studies have indicated that TBS evoked comparable or even greater motor-evoked potentials (MEPs) [11] with longer-lasting effects than conventional rTMS methods [10]. Generally, iTBS is applied to the ipsilesional primary motor cortex to facilitate cortical excitability, while continuous TBS (cTBS) is used to suppress the cortical excitability of the contralesional site [10]. The interhemispheric competition model indicates that cortical excitability decreases in the affected hemisphere following stroke, while transcallosal inhibitory signals from the unaffected hemisphere increase due to cortical hyperexcitability [12]. The increased cortical excitability in the intact hemisphere results in suppression of the ipsilesional hemisphere, which further leads to poor motor recovery in post-stroke patients [13]. Ward, N., *et al* found that the interhemispheric inhibition decreases with time, suggesting that cTBS has limited effect in stroke patients during chronic stage. Additionally, a recent meta-analysis revealed that iTBS has a better effect than cTBS for UL motor recovery in patients with stroke [14]. Spaced TBS with two or more TBS sessions separated by a 10-15 min pause was reported to induce longer-lasting and more consolidate changes in cortical excitability [15, 16]. Therefore, two sessions of iTBS with 600 pulses with a 10-min break to have 1200 pulses in total were given to enhance the modulation effects. Therefore, iTBS with a total of 1200 pulses was administered over the primary motor cortex of the ipsilesional hemisphere to assess its efficacy for improving UL motor function.

VCT aims to target the peripheral mechanisms of stroke recovery, while iTBS aims toward the central mechanisms by modulating cortical excitability [9]. Virtual reality also targets the central mechanisms by inducing cortical reorganization [17], which may cause a synergistic effect when combined with iTBS. A previous study revealed that combining low-frequency rTMS with VR training could improve UL function and quality of life in patients with subacute stroke [18]. Therefore, this study added iTBS on VCT to examine whether combining these two neurotechnologies shows additive effects, and whether central stimulation could augment the effect of peripheral training.

To the best of our knowledge, this is the first randomized controlled trial to propose an innovative protocol adding iTBS on VCT, and to investigate the augmented efficacy of iTBS on VCT for upper limb motor function in patients with stroke. A 15-day intervention was implemented. Based on previous researches, iTBS was reported to reduce spasticity [19, 20] and improve motor function [19, 21]. We hypothesized that post-stroke patients completing a 15-day treatment program with iTBS and VCT have better upper limb motor function than the patients receiving sham stimulation and VCT. Co-primary outcome measures were body function of the affected upper limb, including Modified Ashworth Scale Upper Extremity (MAS-UE) and Fugl-Meyer Assessment Upper Extremity (FMA-UE). Secondary outcome measures were activities and participation of the affected upper limb, including Action Research Arm Test (ARAT), Box and Block Test (BBT), Nine Hole Peg Test (NHPT), Motor Activity Log (MAL), and Stroke Impact Scale (SIS).

Methods

Participants

Patients with stroke were recruited from the rehabilitation ward of Chang Kung Memorial Hospital. Inclusion criteria were: (1) first ever cerebral stroke; (2) under stable condition; (3) unilateral hemiplegia or hemiparesis due to unilateral cerebral stroke; (4) Brunnström stage of the affected upper limb ≥ 3, and (5) 30 to 70 years of age. Exclusion criteria were: (1) brainstem or cerebellar stroke; (2) history of seizure, brain aneurysm or arteriovenous malformation; (3) active psychiatric disease; (4) progressive neurodegenerative disease impairing cognitive function; (5) communicated disorders such as aphasia; (6) severe or active medical problems such as cardiac disease or pneumonia; (7) heavy metal implant; (8) pregnancy, (9) severe visual impairment; and (10) inability to follow instructions. All participants had signed the informed consent. The study was approved by Chang Gung medical foundation institutional review board and was registered under ClinicalTrials.gov ID No. NCT03350087.

Design and experimental procedure

This study was a prospective, double-blinded and randomized controlled trial. Patients were randomly assigned to iTBS or sham stimulation in addition to VCT and were blind to the type of stimulation delivered. Randomized allocation was performed by generating a random sequence on the (https://www.randomizer.org/) website. Figure 1 and 2 illustrate schematic overviews of the randomized allocation and experimental procedure, respectively. Each patient received iTBS or sham stimulation before the 60-minute VCT program on the same day for 15 consecutive working days (3 weeks). To avoid the contamination of physical activities on the effects of TBS, patients were told to avoid any movement of the affected upper limb before, during, and after the stimulation. We try to avoid subjects' physical activities and consolidate the effects of TBS in the period between TBS and VCT. Patients were then moved from the site of TBS stimulation to that of VCT by a wheelchair, and the distance between two sites was around 2 meters. The training of VCT program was started as early as the setting of VCT was completed and the vital signs of patients were checked. In general, it took around 10 minutes between the end of TBS and the beginning of training. Patients were evaluated within 3 days before and after completing the therapy. The outcome measures were administered by raters, occupational therapists, who contacted patients only during assessment and were blind to group assignment. The raters were trained before the experiment and evaluated by the written exam and reliability test. A 10-patient reliability test, measuring both intra-rater and inter-rater reliability, was conducted at 7-day intervals. The intra-rater/inter-rater reliability of the MAS-UE, FMA-UE, BBT and ARAT were analyzed by intra-class correlation as 0.841/0.841, 0.984/0.992, 1.000/0.998, and 0.986/0.998.

Virtual reality-based cycling training

The VCT program comprised a warm-up exercise for 5 minutes, a 10-min weight training for upper limb including muscle strengthening, a 40-min cycling program composed of warm up, strength, and endurance training, and a 5-min cool down exercise. Dr. Hsieh-Ching Chen integrated virtual reality program with arm cycle (BK0010, X-BIKE Fitness Technology Company Limited) to comprise the virtual reality-based cycling system. The setup of the VCT was demonstrated in figure 3. During the training of the VCT program, patients would see themselves controlling the handlebar of a bicycle while riding on the road in different types of sceneries. The visual speed of the virtual scene was altered according to the signal of the cycling speed transmitted to the computer, increasing participants' interest and motivation. Participants underwent low to moderate resistance and high revolutions per minute cycling exercise during the VCT program. Participants were encouraged to raise rpm during the program, aiming for the target heart rate based on the Karvonen Formula [22]. Thus, to ensure that participants achieved the target heart rate, the resistance was adjusted according to each participant's clinical condition. To ensure participants' safety, blood pressure, heart rate and oxygen saturation were monitored throughout the whole training program.

Intermittent theta burst stimulation paradigm

iTBS was delivered over the hand motor area of the affected hemisphere by a handheld 70-mm standard, figure-of-eight coil connected to a MagPro X100 package (Magventure, USA). The optimal coil positioning over the scalp region was the motor hot spot, where the transcranial magnetic stimulation (TMS) evoked the largest MEP in the contralateral first dorsal interosseous (FDI) muscle with the patient at rest. Active motor threshold (AMT) was measured before each intervention, and was defined as the minimum TMS intensity required to evoke MEPs ($\geq$200 μV) in at least 5 of 10 successive trials from the slightly contracted (approximately 10-20% of maximal strength) FDI muscle. True stimulation was applied over the identified motor hot spot at an intensity of 80% AMT, with the coil placed tangentially to the skull, at a 45° angle to the midsagittal axis, generating posterior-anterior current flow at targeted area in the brain. If MEPs could not be elicited, stimulation was applied to the mirror site of the motor hot spot over the unaffected hemisphere, as previous studies [19, 20], at an intensity of 70% RMT. Sham stimulation was administered at the same site with identical flip coil, resulting in a 78% output elicited by non-flip side, at a lower intensity (60% AMT) equivalent to 46.8% AMT [23]. The sham stimulation with intensity lower than 70% AMT has no effect on MEPs, as demonstrated by a previous study [24], but produces indistinguishable sensation and sound compared to real stimulation. Several previous studies administered a similar sham stimulation method, and found it to be useful [19, 23, 25]. All patients were seated comfortably with their hands as relaxed as possible throughout the experiment after the AMT was recorded. An iTBS session comprised 2-second train of bursts, containing three pulses at 50Hz, repeated at intervals of 200ms, every 10 seconds for 20 times (a total of 600 pulses). Learning from studies on spaced TBS [15, 16], two sessions of iTBS were applied with a 10-to-15-min break for a total of 1200 pulses to consolidate and enhance the effects. Patients were instructed to rest and not to move during the 10-min break in order to minimize cofounding factors and not to disrupt any ongoing plasticity [26]. Real or sham iTBS was delivered for 15 consecutive work days.

Outcome measures

Based on the conceptual framework of International Classification of Functioning, Disability and Health (ICF) [27], body function, activities and participation of upper limb motor function before and after the intervention were evaluated using seven measures, namely MAS-UE, FMA-UE, ARAT, BBT, and NHPT, MAL, and SIS. Among these aspects, primary outcome measure was the domain of body function, and secondary outcome measures were the domains of activities and participation.

Co-primary outcome measures were the improvement of body function, measuring by MAS-UE and FMA-UE. MAS-UE, which is scored from 0 to 4 (0, 1, 1+, 2, 3, 4), was used to assess UL spasticity and resistance during passive joint movement [28, 29]. The affected finger flexor muscles, wrist and elbow were evaluated. These MAS-UE scores were summed to represent the UL spasticity, with 1+ calculated as 1.5. FMA-UE is a performance-based scale, particularly for patients with stroke, to assess sensorimotor function including motor function, joint function, sensation and balance [30]. This study only evaluated the UL motor function of FMA.

The improvement of activity was evaluated using ARAT, BBT, NHPT and MAL. ARAT measures UL motor function, and comprises 19 items divided into 4 subsets: grasp, grip, pinch, and gross movement (GM) [31]. BBT is a functional test to measure unilateral gross manual dexterity [32], in which patients have to move as many blocks from one box to another box as possible in 60 seconds only by the affected hand, which task requires grasping, transporting and releasing. NHPT is a timed test performed to evaluate manual dexterous function [33], in which patients insert nine pegs into nine holes of the pegboard and then pick them up as quickly as possible. Because the patients with severe motor impairment might be unable or needed a long time to complete the task, patients were asked to perform NHPT within two minutes. To distinguish the ability of the patients who could not complete the task in two minutes, the number of pegs being placed and removed was calculated. The outcome variable is the number of pegs/minute, and more pegs/minute indicates better dexterity. MAL was assessed to determine patients' real life functional performance involving the affected arm based on 14 daily activities [34], including amount of use and quality of movement.

SIS, a patient-reported questionnaire, was performed to evaluate participation in patients with stroke [35]. SIS is a measure specific in patients with stroke, and higher scores reflect greater participation.

Statistical analysis

All statistical analyses were conducted with SPSS version 21 (SPSS Inc., Chicago, Illinois). To determine the baseline between-group differences of demographic characteristics, Chi-square tests were applied for the categorical variables and independent two-sample *t*-tests were conducted for the continuous variables. Paired *t*-tests were run to test whether each groups showed significant improvement after the therapy. Analysis of covariance (ANCOVA) was conducted to control the variance in the covariate, and was applied to assess whether the iTBS group had greater therapeutic effect than the control group. The pre-test scores were the covariates, the post-test scores were the dependent variables, and the group was the independent variable. The effect size (η^2) was calculated to assess the degree of between-group differences, which were classified as large ($\eta^2 \geq 0.138$), moderate ($0.059 \leq \eta^2 < 0.138$), and small ($0.01 \leq \eta^2 < 0.059$) [36]. Statistical significance level was set at $p < 0.05$ (one-tailed) [37] for all analyses under directional hypothesis [38].

Results

A total of 684 patients were screened, among whom 657 patients were excluded and 3 patients declined to participate. Twenty-four patients were randomly allocated to the iTBS or the control group, and one patient in the iTBS group withdrew from the study. Ultimately, 12 patients in the iTBS group and 11 patients in the control group completed the study course. The time since stroke onset of all the patients was greater than 3 weeks. The demographic and clinical data did not differ between two groups (Table 1). Although the NIHSS in the sham iTBS and VCT group is greater than iTBS and VCT group, it did not reach significant differences. All patients could tolerate the intervention without significant adverse effects throughout the study. Throughout the treatment course, only one patient mentioned upper limbs muscle soreness after receiving VCT training program. The discomforts relieved after taking rest and ice packing. No significant baseline between-group differences in outcome measures were observed (Table 2).

Primary outcomes

Body function

Paired *t*-tests revealed significant improvement after the intervention in both groups in FMA-UE (control: p = 0.002; iTBS: p = 0.018), while only the iTBS group showed significant improvement in MAS-UE (control: p = 0.392; iTBS: p = < 0.001). After the intervention, ANCOVA showed that the iTBS group induced significantly greater gains than the control group in MAS-UE with a large effect size (p = 0.004, η^2=0.302), but did not have significantly greater gains in FMA-UE (p = 0.203, η^2 = 0.035) (Table 3).

Secondary outcomes

Activity

After the intervention, the iTBS group showed significant improvement in GM and grip domains of ARAT (GM: p = 0.002; Grasp: p = 0.246; Grip: p = 0.045; Pinch: p = 0.066). The control group showed significant improvement only in the GM domain after the intervention. (GM: p = 0.006; Grasp: p = 0.096; Grip: p = 0.129; Pinch: p = 0.171). ANCOVA results revealed that all the domains of ARAT did not differ between two groups (GM: p = 0.086, η^2 = 0.092; grasp: p = 0.139, η^2 =0.059; grip: p = 0.153, η^2 = 0.053; pinch: p = 0.117, η^2 =0.07).

In BBT, paired t-tests revealed that only the iTBS group had significant improvement after the intervention (control: p = 0.387; iTBS: p = 0.030), and ANCOVA showed that the iTBS group had no greater gains than the sham group (p = 0.083, η^2=0.094). In NHPT, paired t-tests revealed that only the iTBS group had significant improvement after the intervention (control: p = 0.198; iTBS: p = 0.013), and ANCOVA showed greater gains in the iTBS group than the control group with a moderate effect size (p = 0.045, η^2=0.137).

In MAL, the iTBS group showed significant improvement after the intervention, and the sham group had no significant improvement in MAL (control: MAL-AOU: p = 0.079, MAL-QOM: p = 0.256; iTBS: MAL-AOU: p = 0.012, MAL-QOM: p = 0.019). ANCOVA revealed no significant between-group differences in the gains following the intervention in MAL (MAL-AOU: p = 0.065, η^2=0.272; MAL-QOM: p = 0.054, η^2=0.124).

Participation

In SIS, paired t-tests showed that only the iTBS group had significant improvement after the intervention (control: p = 0.333; iTBS: p < 0.001), and ANCOVA revealed that iTBS group had greater gains than the control group, with a large effect (p = 0.002, η^2=0.339).

Discussion

To the best of our knowledge, this is the first exploratory trial to test whether TBS had augmented efficacy on VCT for upper limb function. In the current study, iTBS induced significantly greater gains in the MAS-UE, NHPT and SIS than sham stimulation. However, the changes in FMA-UE, ARAT, BBT, and MAL did not differ between the two groups. These findings indicate that iTBS augments the effect of VCT on reducing spasticity, improving manual dexterity, and ameliorating participation. It is worth noting that this study demonstrated iTBS had a promising additional benefit on VCT to improve manual dexterity, despite it was hard to reclaim after stroke. Since this is the first study to perform iTBS on VCT in stroke patients, our findings were compared with those of studies adding iTBS on other neurorehabilitation program.

Experimental results reveal that the iTBS group showed greater reduction in spasticity than the sham group in stroke patients. Our findings were consistent with those of a randomized controlled trial indicating that iTBS showed a significant reduction of spasticity in patients with chronic stroke [19], and were also compatible with another study demonstrating that a single session of iTBS significantly reduced UL spasticity transiently in patients with acute and chronic stroke [20]. The minimal clinically important differences (MCID) of MAS of large and medium effect size were reported to be 0.76 and 0.48, respectively [39]. Based on the equation provided in the previous study [39], the MCID of MAS of small effect size (0.2 standard deviations) was 0.19. Despite the mean improvement after receiving iTBS and VCT in the study was 0.22, which did not meet the medium effect size, it reached a small effect size. Overall, iTBS showed augmented effect on VCT for reducing spasticity in stroke patients.

Spasticity, a phenomenon of the upper motor neuron syndrome, is a common cause of long-term disability in stroke patients. The postulated pathophysiology of spasticity is that lesions of upper motor neuron impair the supraspinal inhibitory inputs, leading to an increased excitability of α and γ motor neurons, and of the interneurons at the spinal level, ultimately causing spasticity [40, 41]. Therefore, facilitatory rTMS and iTBS had been applied to lower spasticity in patients with a number of neurologic disorders [19-20, 42-47] by modulating the excitability of cortical motor neurons. In addition, it is increasingly accepted that iTBS may modulate cortical excitability by inducing the long-term potential-like (LTP-like) plasticity changes [10, 48-49], and the persistently increasing neural activity may project to inhibitory corticospinal synapses. Additionally, iTBS may also alter the level of endogenous transmitters involving in synaptic plasticity [46, 50] such as γ-aminobutyric acid [51], glutamate [52] and dopamine [53]. The mechanism for the anti-spastic effect of iTBS remains unclear to date, and further neurophysiological studies are warranted to identify the underlying mechanism.

In the current study, both groups showed significant improvement in FMA after the intervention, but the changes after the intervention revealed no significant differences between the iTBS and sham group. One possible explanation is that virtual reality (VR) itself generates an enriched environment providing sensorimotor stimulation and leads to improvement in upper limb motor function [54-56]. Conversely, arm cycling involves repetitive bilateral arm training and is able to improve upper limb motor function [57]. Our findings were partially consistent with previous studies [19, 58]. Hsu *at el* found that six patients with subacute ischemic stroke receiving iTBS had measurable improvement in the proximal UL motor function compared with the other six patients receiving sham stimulation [58]. Chen et al revealed that iTBS had significant effect on upper limb motor function measured by the FMA in patients with chronic stroke [19]. Zheng et al found that combining low-frequency rTMS and VR training showed prominent effects at the 2nd, 3rd, and 4th week after the intervention [18]. The application of iTBS over the ipsilesional hemisphere was based on the vicariation theory, proposing that surviving neurons situated at the peri-infarct area may be reorganized and substitute the function of the stroke region [59, 60]. Since upper limb motor recovery relies on the vicarious capacity of the primary motor cortex (M1), facilitation of the affected hemisphere may arouse compensatory neural plasticity adjacent to the lesion and rebalance cortical excitability between hemispheres. Overall, our study revealed that iTBS may have no additionally augmented effect on VCT in UL impairment.

In the current study, only the iTBS and VCT group showed significant improvement after the intervention in both NHPT and BBT, while the VCT alone did not. Furthermore, iTBS and VCT induced greater gains than VCT alone significantly in NHPT. These results partially resembled those of some previous studies [19, 21, 61]. Talelli et al reported that 6 patients with chronic stroke had shorter simple reaction times of gripping tasks after iTBS than after sham stimulation [21]. Malcolm *et al* demonstrated that the group receiving rTMS as an adjuvant therapy to constraint-induced therapy had greater gains than the sham stimulation group in BBT at 6 months [61]. A more recent study by Chen *et al* reported that iTBS significantly improved the performance in BBT in 22 patients with chronic stroke [19]. These variable findings may be owing to different patient characteristics, since inter-individual response variability following iTBS had been observed [59]. Stimulation protocols, intensity and location may also influence the effect of rTMS on neural activity. A previous study found iTBS may potentially increase M1 receptiveness to sensory inputs from cortical areas [62]. These effects may provide a permissive environment for rebalancing corticomotor excitability and cortical reorganization, which ameliorates planning, coordination and execution of the movement. Furthermore, the motor recovery after stroke is generally thought to follow a proximal to distal gradient, and that gross motor function usually recovers better than fine motor function [63-65]. However, our results indicate that iTBS combined with VCT may improve the fine motor function. In summary, iTBS showed a promising additional benefit on VCT for the recovery of manual dexterity.

After the intervention, the iTBS and VCT group showed significant improvement in gross and fine motor domains, while the VCT alone group only showed significant improvement in gross motor domain. However, the iTBS and VCT group showed no greater gains than the VCT alone group. A previous study by Ackerley *et al* found that iTBS priming with physical therapy, but not sham stimulation, enhanced the improvement in ARAT, and could be maintained for one month in 18 patients with chronic stroke [66]. Chen *et al* reported that iTBS showed greater improvement than the control group in fine motor domains including pinch, grasp, and grip, but not in gross motor domain [19]. These findings could be explained by different neurorehabilitation protocols. Gross motor movement mainly involves shoulder and elbow, which were the major parts trained by VCT. Although there was no significant difference in the ARAT change between groups, patients receiving iTBS and VCT in our studies had significant improvement in the gross motor domain of ARAT as comparing to the baseline. In current study, treatment with iTBS combined VCT might show the potential to have benefits on both gross and fine motor recovery, although iTBS had no augmented efficacy on VCT to improve all the domains of motor function in ARAT.

Although this study demonstrated that only the iTBS and VCT combined group showed significant improvement in MAL after the intervention, the changes in the MAL after intervention did not achieve significant differences between 2 groups. Malcolm *et al* found that the changes after the intervention in both MAL-AOU and MAL-QOM did not differ between the ten sessions of rTMS and sham stimulation at time points of 2 weeks and 6 months [61]. In addition, Chen et al also indicated that the iTBS group had no greater improvement than the sham group in MAL-AOU and MAL-QOM [19]. To explain current result, the learned non-use phenomenon may play an important role [67], because patients may not be aware of the residual motor function of the affected UL [68]. Moreover, it might take a longer time to overcome the compensatory strategy after stroke. To sum up, iTBS showed no augmented efficacy on VCT in increasing actual use of the affected UL.

The present study revealed that only the iTBS and VCT group showed significant improvement in SIS after the intervention. Furthermore, the iTBS and VCT group had greater gains than the VCT alone group. SIS comprises various aspects including motor function, ADL, mobility, emotion, communication, memory and thinking, and participation. To our best knowledge, this is the first study to assess SIS in patients with stroke after iTBS. However, our findings were not compatible with those of a previous study, which reported that rTMS as an adjuvant therapy to task-oriented training showed no greater gains than sham stimulation in SIS [69]. These variable findings may due to different protocols. To further explore the result, the therapeutic effect in different aspects of SIS was analyzed. The iTBS group had greater gains than the VCT alone group in the aspects of mobility, hand function, and participation. A previous study reported that arm cycling training improved walking ability and balance [70]. These findings may result from enhancing interlimb connectivity, reflex control, and locomotor central pattern-generating networks, controlling both arm cycling and walking [70]. Therefore, the positive effects of arm cycling may further improve the participation in the mobility domain. As for the aspect of participation, among the eight questions, active recreation, the role as a family member, and the ability to help others were self-reported to have greater gains in the iTBS group than the sham group. One explanation was that theta bust stimulation was reported as anti-depression treatment [71, 72], and recovering from post-stroke depression might enable the patients to communicate more effective with others. However, the stimulation site for depression is different from that for motor impairment. Therefore, further studies are warranted to identify the underlying mechanism. In conclusion, since this study found that iTBS can augment the effect of VCT on improving manual dexterity and reducing spasticity, iTBS can also be reasonably considered to augment the effect of VCT on enhancing participation.

This study has several limitations. First, the sample size was relatively small, and a large-scale survey is warranted to confirm the clinical benefits. Second, no follow up for the long-term effect of iTBS was performed, hence further studies should also trace for the lasting efficacy. Third, the study recruited patients with age only between 30 to 70 years, and therefore the findings in the study may not extend to younger or older patients. Fourth, no multiple comparisons were conducted to control type II errors [73], considering the fact that this is a small sample-sized study and the nature of the study was to explore the efficacy of a novel intervention.

Conclusions

Applying iTBS over the ipsilesional hemisphere had augmented efficacy on VCT in reducing spasticity, improving manual dexterity, and increasing participation in daily life. Notably, this study demonstrated that iTBS had promising additional benefit on VCT to enhance manual dexterity. Additionally, no patients experienced significant acute side effects after receiving iTBS in all patients. In conclusion, iTBS may be a promising and safe treatment option as an adjuvant therapy that could augment the therapeutic effects of neurorehabilitation in stroke patients. A further larger-scale study is warranted to verify the results.

Abbreviations

ADL: Activities of daily living; AMT: Active motor threshold; AOU: Amount of Use scale; ARAT: Action Research Arm Test; BBT: Box and Block test; cTBS: Continuous TBS; FMA-UE: Fugl-Meyer Assessment Upper Extremity; ICF: International Classification of Functioning, Disability, and Health framework; iTBS: Intermittent TBS; M1: Primary motor cortex; MAL: Motor activity log; MAS-UE: Modified Ashworth scale Upper Extremity; MEPs: Motor-evoked potentials; NHPT: Nine Hole Peg Test; QOM: Quality of Movement scale; RCT: Randomized controlled trial; rTMS: Repetitive transcranial magnetic stimulation; SIS: Stroke Impact Scale; TBS: Theta burst stimulation; UL: Upper limb; VCT: Virtual reality-based cycling training ; VR: Virtual reality

Declarations

Ethics approval and consent to participate

All participants gave their written informed consent prior to participate in this study. Approval of this study was obtained from the Institutional Review Board of Chang Gung Memorial Hospital, Taiyuan, Taiwan.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Ministry of Science and Technology (MOST 105-2314-B-182-020-MY3, 108–2314-B-182-043), and Chang Gung Medical Foundation (CMRPG3D1461-3) in Taiwan. These funding agencies did not involve in the design of the study, data collection and analysis, and drafting of the manuscript.

Authors' contributions

YHC and CCL contributed equally to the manuscript. YHC and CCL analyzed and interpreted the data, and drafted the first manuscript. CCL contributed to the design of the study, project management, data collection, and revision of the manuscript. YZH instructed the TBS protocol, analyzed and interpreted the data. HCC contributed to software and hardware integration, and data analyses. CYW and KCL involved in the data collection, analysis and interpretation. All authors involved in the revision of the study and approved the final manuscript.

Acknowledgements

We thank the patients who participated in this study.

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References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blahae MJ, et al. Executive summary: heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129(3):399-410.
2. Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. Arch Phys Med Rehabil. 2002;83(11):1629-37.
3. Holden MK. Virtual environments for motor rehabilitation. Cyberpsychol Behav. 2005;8(3):187-211.
4. Vidoni E, Acerra NE, Dao E, Meehan SK, Boyd LA. Role of the primary somatosensory cortex in motor learning: an rTMS study. Neurobiol Learn Mem. 2010;93(4):532-9.
5. Parlow SE, Dewey D. The temporal locus of transfer of training between hands: an interference study. Behav Brain Res. 1991;46(1):1-8.
6. Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation-a clinical review. J Rehabil Res Dev. 1999;36(3):237-51.
7. Bütefisch C, Hummelsheim H, Denzler P, Mauritz KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. J Neurol Sci. 1995;130(1):59-68.
8. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. JAMA. 2004;292(15):1853-61.

9. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci. 2007;8(7):559-67.
10. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;45(2):201-6.
11. Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, et al. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol. 2011;105(5):2150-6.
12. Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. Neurorehabil Neural Repair. 2009;23(7):641-56.
13. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003;126(Pt 11):2476-96.
14. Zhang L, Xing G, Fan Y, Guo Z, Chen H, Mu Q. Short-and long-term effects of repetitive transcranial magnetic stimulation on upper limb motor function after stroke: a systematic review and meta-analysis. Clin Rehabil. 2017;31(9):1137-53.
15. Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SM, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci. 2014;34(20):6849-59.
16. Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. Eur J Neurosci. 2012;35(1):125-34.
17. You SH, Jang SH, Kim YH, Hallett M, Ahn SH, Kwon YH, et al. Virtual reality–induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. Stroke. 2005;36(6):1166-71.
18. Zheng CJ, Liao WJ, Xia WG. Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trail. J Huazhong Univ Sci Technolog Med Sci. 2015;35(2):248-54.
19. Chen YJ, Huang YZ, Chen CY, Chen CL, Chen HC, Wu CY, et al. Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. BMC Neurol. 2019;19(1):69.
20. Kim DH, Shin JC, Jung S, Jung TM, Kim DY. Effects of intermittent theta burst stimulation on spasticity after stroke. Neuroreport. 2015;26(10):561-6.
21. Talelli P, Greenwood RJ, Rothwell JC. Exploring theta burst stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol. 2007;118(2):333-42.
22. Karvonen J, Vuorimaa T. Heart rate and exercise intensity during sports activities. Pract Appl Sports Med. 1988;5(5):303-11.
23. Huang YZ, Lu CS, Rothwell JC, Lo CC, Chuang WL, Weng YH, et al. Modulation of the disturbed motor network in dystonia by multisession suppression of premotor cortex. PLoS One. 2012;7(10):e47574.
24. Huang YZ, Rothwell JC, Lu CS, Wang J, Weng YH, Lai SC, et al. The effect of continuous theta burst stimulation over premotor cortex on circuits in primary motor cortex and spinal cord. Clin

Neurophysiol. 2009;120(4):796-801.

25. Chuang WL, Huang YZ, Lu CS, Chen RS. Reduced cortical plasticity and GABAergic modulation in essential tremor. Mov Disord. 2014;29(4):501-7.
26. Huang YZ, Rothwell JC, Edwards MJ, Chen RS. Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. Cereb Cortex. 2008;18(3):563-70.
27. Stucki G. International Classification of Functioning, Disability, and Health (ICF): a promising framework and classification for rehabilitation medicine. Am J Phys Med Rehabil. 2005;84(10):733-40.
28. Meseguer-Henarejos AB, Sánchez-Meca J, López-Pina J, Carles-Hernández R. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2018;54(4): 576-90.
29. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67(2):206-7.
30. Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair. 2002;16(3):232-40.
31. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. Neurorehabil Neural Repair. 2008;22(1):78-90.
32. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the box and block test of manual dexterity. Am J Occup Ther. 1985;39(6):386-91.
33. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole peg test of finger dexterity. Occup Ther J Res. 1985;5(1):24-38.
34. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. Stroke. 2005;36(11):2493-6.
35. Duncan PW, Bode RK, Lai SM, Perera S, Glycine Antagonist in Neuroprotection Americans Investigators. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil. 2003;84(7):950-63.
36. Cohen J. Statistical power analysis for the behavioral sciences. Academic Press; 2013. New York
37. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
38. Kock N. One-tailed or two-tailed P values in PLS-SEM? Int J Electron Commer. 2015;11(2):1-7.
39. Chen CL, Chen CY, Chen HC, Wu CY, Lin KC, Hsieh YW, et al. Responsiveness and minimal clinically important difference of Modified Ashworth Scale in patients with stroke. Eur J Phys Rehabil Med. 2019;55(6):754-60.

40 Mukherjee A, Chakravarty A. Spasticity mechanisms - for the clinician. Front Neurol. 2010;1(149).

41. Sheean G. The pathophysiology of spasticity. Eur J Neurol. 2002;9(Suppl 1):3-9.
42. Korzhova J, Bakulin I, Sinitsyn D, Poydasheva A, Suponeva N, Zakharova M, et al. High-frequency repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation for spasticity management in secondary progressive multiple sclerosis. Eur J Neurol. 2019;26(4):680-e44.

43. Gharooni AA, Nair KPS, Hawkins D, Scivill I, Hind D, Hariharane R. Intermittent theta-burst stimulation for upper-limb dysfunction and spasticity in spinal cord injury: a single-blind randomized feasibility study. Spinal Cord. 2018;56(8):762-8.
44. Nardone R, Langthaler PB, Orioli A, Höller P, Höller Y, Frey VN, et al. Effects of intermittent theta burst stimulation on spasticity after spinal cord injury. Restor Neurol Neurosci. 2017;35(3):287-94.
45. Boutière C, Rey C, Zaaraoui W, Le Troter A, Rico A, Crespy L, et al. Improvement of spasticity following intermittent theta burst stimulation in multiple sclerosis is associated with modulation of resting-state functional connectivity of the primary motor cortices. Mult Scler. 2017;23(6):855-63.
46. Mori F, Codecà C, Kusayanagi H, Monteleone F, Boffa L, Rimano A, et al. Effects of intermittent theta burst stimulation on spasticity in patients with multiple sclerosis. Eur J Neurol. 2010;17(2):295-300.
47. Valle AC, Dionisio K, Pitskel NB, Pascual-Leone A, Orsati F, Ferreira MJL, et al. Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. Dev Med Child Neurol. 2007;49(7):534-8.
48. Huang YZ, Lu MK, Antal A, Classen J, Nitsche M, Ziemann U, et al. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. Clin Neurophysiol. 2017;128(11):2318-29.
49. Suppa A, Huang YZ, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. Brain Stimul. 2016;9(3):323-35.
50. Sala C, Piëch V, Wilson NR, Passafaro M, Liu G, Sheng M. Regulation of dendritic spine morphology and synaptic function by Shank and Homer. Neuron. 2001;31(1):115-30.
51. Stagg CJ, Wylezinska M, Matthews PM, Johansen-Berg H, Jezzard P, Rothwell JC, et al. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. J Neurophysiol. 2009;101(6):2872-7.
52. Michael N, Gösling M, Reutemann M, Kersting A, Heindel W, Arolt V, et al. Metabolic changes after repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex: a sham-controlled proton magnetic resonance spectroscopy (1H MRS) study of healthy brain. Eur J Neurosci. 2003;17(11):2462-8.
53. Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain. 2003;126(Pt 12):2609-15.
54. Fluet GG, Deutsch JE. Virtual reality for sensorimotor rehabilitation post-stroke: the promise and current state of the field. Curr Phys Med Rehabil Rep. 2013;1(1):9-20.
55. Bao X, Mao Y, Lin Q, Qiu Y, Chen S, Li L, et al. Mechanism of kinect-based virtual reality training for motor functional recovery of upper limbs after subacute stroke. Neural Regen Res. 2013;8(31):2904-13.
56. Adamovich SV, Fluet GG, Tunik E, Merians AS. Sensorimotor training in virtual reality: a review. NeuroRehabilitation. 2009;25(1):29-44.
57. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke. 2000;31(10):2390-5.

58. Hsu YF, Huang YZ, Lin YY, Tang CW, Liao KK, Lee PL, et al. Intermittent theta burst stimulation over ipsilesional primary motor cortex of subacute ischemic stroke patients: a pilot study. Brain Stimul. 2013;6(2):166-74.
59. Lopez-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-Del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul. 2014;7(3):372-80.
60. Jaillard A, Martin CD, Garambois K, Lebas JF, Hommel M. Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. Brain. 2005;128(5):1122-38.
61. Malcolm MP, Triggs WJ, Light KE, Rothi LJG, Wu S, Reid K, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. Am J Phys Med Rehabil. 2007;86(9):707.
62. Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Priming sensorimotor cortex to enhance task-specific training after subcortical stroke. Clin Neurophysiol. 2014;125(7):1451-8.
63. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neur Repair. 2002;16(3):232-40.
64. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13-31.
65. George SH, Rafiei MH, Borstad A, Adeli H, Gauthier LV. Gross motor ability predicts response to upper extremity rehabilitation in chronic stroke. Behav Brain Res. 2017;333:314-22.
66. Ackerley SJ, Byblow WD, Alan Barber P, MacDonald H, McIntyre-Robinsone A. Primed physical therapy enhances recovery of upper limb function in chronic stroke patients. Neurorehabil Neural Repair. 2016;30(4):339-48.
67. Taub E, Uswatte G, Mark VW, Morris DMM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-55.
68. Sterr A, Freivogel S, Schmalohr D. Neurobehavioral aspects of recovery: assessment of the learned nonuse phenomenon in hemiparetic adolescents. Arch Phys Med Rehabil. 2002;83(12):1726-31.
69. Higgins J, Koski L, Xie H. Combining rTMS and task-oriented training in the rehabilitation of the arm after stroke: a pilot randomized controlled trial. Stroke Res Treat. 2013;2013(539146).
70. Kaupp C, Pearcey GEP, Klarner T, Sun Y, Cullen H, Barss TS, et al. Rhythmic arm cycling training improves walking and neurophysiological integrity in chronic stroke: the arms can give legs a helping hand in rehabilitation. J Neurophysiol. 2018;119(3): 1095-112.
71. Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain. 2014;137(7):2088-98.
72. Chung SW, Hoy KE, Fitzgerald PB. Theta-burst stimulation: A new form of TMS treatment for depression? Depress Anxiety. 2015;32(3):182-92.
73. Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Medical Res Methodol. 2002;2(1):1-4.

Tables

Table 1 Demographic and clinical characteristics

	sham iTBS + VCT	iTBS + VCT	*P*-value
Age	48.95 ± 9.63	54.36 ± 10.56	0.215[a]
Gender			0.317[b]
Male	10 (90.9%)	8 (66.7%)	
Female	1 (9.1%)	4 (33.3%)	
Onset time (month)	7.99 ± 5.41	5.01 ± 4.39	0.160[a]
Stroke type			0.193[b]
Infarction	2 (18.2%)	6 (50%)	
Hemorrhage	9 (81.8%)	6 (50%)	
Stroke side			
Right	4 (36.4%)	5 (41.7%)	1.000[b]
Left	7 (63.6%)	7 (58.3%)	
MEP			0.879[b]
Positive	7 (63.6%)	8 (66.7%)	
Negative	4 (36.4%)	4 (33.3%)	
Aphasia			0.640[b]
Yes	3 (27.3%)	2 (16.7%)	
No	8 (72.7%)	10 (83.3%)	
NIHSS	13.55 ± 2.38	11.92 ± 1.73	0.073[a]

Data are presented as mean ± standard deviation or number (%)

[a] independent two-sample *t* tests; [b] Chi-square tests

iTBS: intermittent theta burst stimulation, MEP: motor evoked potential,

NIHSS: National Institutes of Health Stroke Scale

Table 2 Baseline of outcome measures

	sham iTBS + VCT	iTBS + VCT	*P*-value
MAS-UE	0.94 ± 0.69	0.87 ± 0.54	0.765
FMA-UE	34.55 ± 18.34	43.58 ± 15.35	0.213
ARAT	17.09 ± 18.11	25.75 ± 22.69	0.326
GM	4.73 ± 1.68	5.33 ± 2.87	0.548
Grasp	5.55 ± 6.65	8.75 ± 8.01	0.311
Grip	3.00 ± 4.31	5.42 ± 5.16	0.239
Pinch	3.82 ± 6.31	6.25 ± 7.40	0.408
BBT	11.40 ± 16.02	18.72 ± 18.84	0.328
NHPT[a]	4.02 ± 8.82	7.86 ± 11.88	0.395
MAL (AOU)	42.64 ± 31.04	33.92 ± 42.40	0.583
MAL (QOM)	46.55 ± 40.89	35.17 ± 42.58	0.521
SIS	199.09 ± 21.40	200.50 ± 29.37	0.897

Data are presented as mean ± standard deviation

iTBS: intermittent theta burst stimulation, VCT: virtual reality-based cycling training, MAS-UE: Modified Ashworth Scale Upper Extremity, FMA-UE: Fugl-Meyer Assessment Upper Extremity, ARAT: Action Research Arm Test, GM: Gross Movement, BBT: Box and Block test, NHPT: Nine Hole Peg Test, MAL(AOU): Motor Activity Log (Amount of Use), MAL (QOM): Motor Activity Log (Quality of Movement), SIS: Stroke Impact Scale

[a] The unit of NHPT is number of pegs/minute

Table 3 Descriptive and inferential statistics and analysis of outcome measures

Variables	sham iTBS + VCT (paired *t*-tests)			iTBS + VCT (paired *t*-tests)			ANCOVA	
	Pre-Tx	Post-Tx	*P* value	Pre-Tx	Post-Tx	*P* value	*P* value	η^2
MAS-UE	0.94 ± 0.69	0.97 ± 0.63	0.392	0.87 ± 0.54	0.65 ± 0.50	< 0.001†	0.004†	0.302
FMA-UE	34.55 ± 18.34	40.64 ± 16.83	0.002†	43.58 ± 15.35	47.17 ± 16.30	0.018*	0.203	0.035
ARAT	17.09 ± 18.11	18.27 ± 18.91	0.042*	25.75 ± 22.69	30.42 ± 22.38	0.038*	0.084	0.093
GM	4.73 ± 1.68	5.36 ± 1.80	0.006†	5.33 ± 2.87	6.50 ± 2.88	0.002†	0.086	0.092
Grasp	5.55 ± 6.65	5.27 ± 6.77	0.096	8.75 ± 8.01	9.50 ± 7.74	0.246	0.139	0.059
Grip	3.00 ± 4.31	3.55 ± 4.55	0.129	5.42 ± 5.16	6.83 ± 5.38	0.045*	0.153	0.053
Pinch	3.82 ± 6.31	4.09 ± 6.33	0.171	6.25 ± 7.40	7.58 ± 7.56	0.066	0.117	0.070
BBT	11.40 ± 16.02	11.88 ± 13.74	0.387	18.72 ± 18.84	21.96 ± 19.50	0.030*	0.083	0.094
NHPT[a]	4.02 ± 8.82	4.56 ± 7.92	0.198	7.86 ± 11.88	11.40 ± 13.86	0.013*	0.045*	0.137
MAL (AOU)	42.64 ± 31.04	36.55 ±22.06	0.079	33.92 ± 42.40	42.25 ± 43.93	0.012*	0.065	0.272
MAL (QOM)	46.55 ± 40.89	42.82 ±32.96	0.256	35.17 ±	42.83 ± 43.39	0.019*	0.054	0.124

				42.58				
SIS	199.09 ± 21.40	200.45 ± 17.50	0.333	200.50 ± 29.37	215.58 ± 31.08	< 0.001†	0.002†	0.339

Data are presented as mean ± standard deviation

iTBS: intermittent theta burst stimulation, VCT: virtual reality-based cycling training, MAS-UE: Modified Ashworth Scale Upper Extremity, FMA-UE: Fugl-Meyer Assessment Upper Extremity, ARAT: Action Research Arm Test, GM: Gross Movement, BBT: Box and Block test, NHPT: Nine Hole Peg Test, MAL(AOU): Motor Activity Log (Amount of Use), MAL (QOM): Motor Activity Log (Quality of Movement), SIS: Stroke Impact Scale

* $p < 0.05$; † $p < 0.01$

[a] The unit of NHPT is number of pegs/minute

Figures

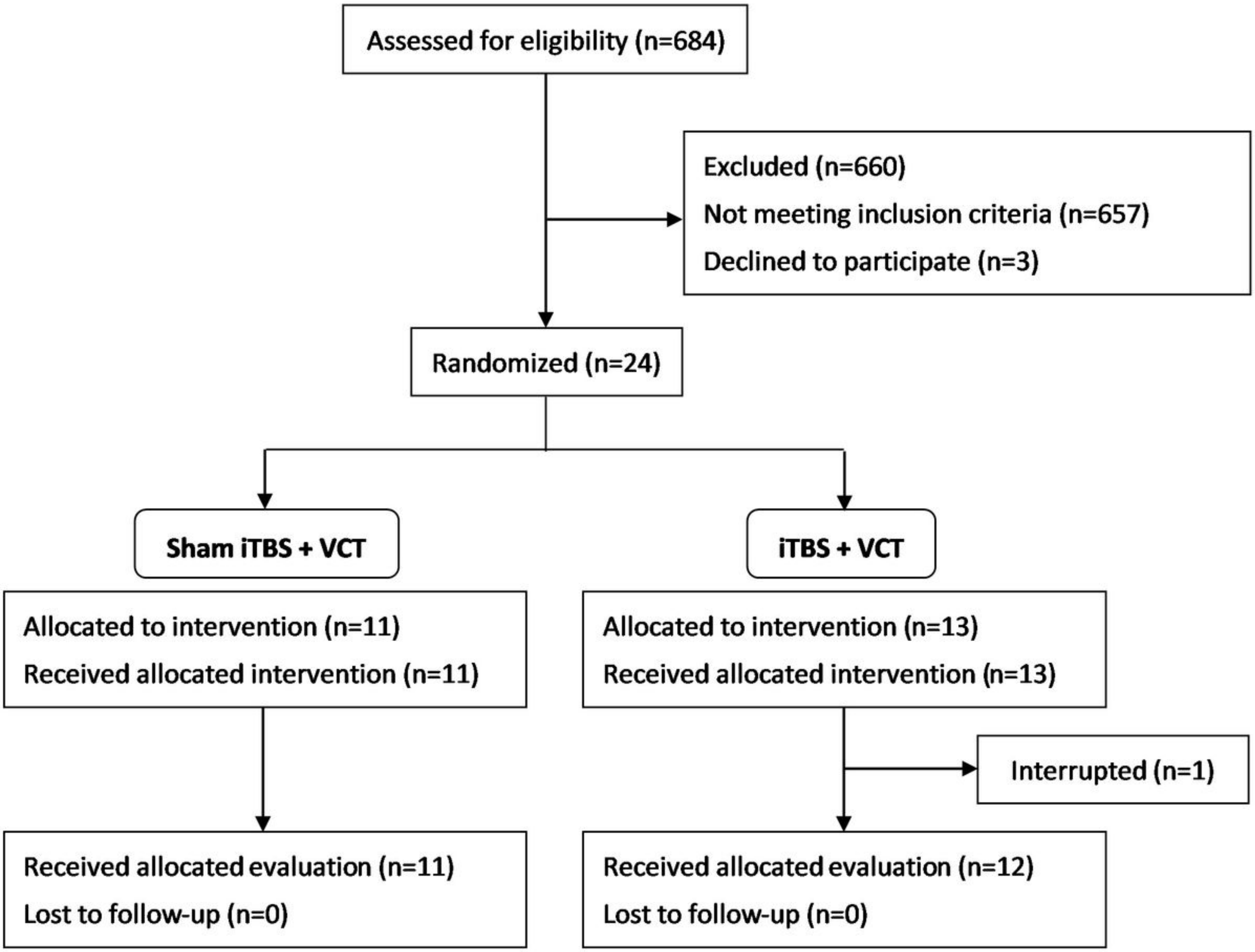

Figure 1

Flow diagram of recruitment and randomized allocation

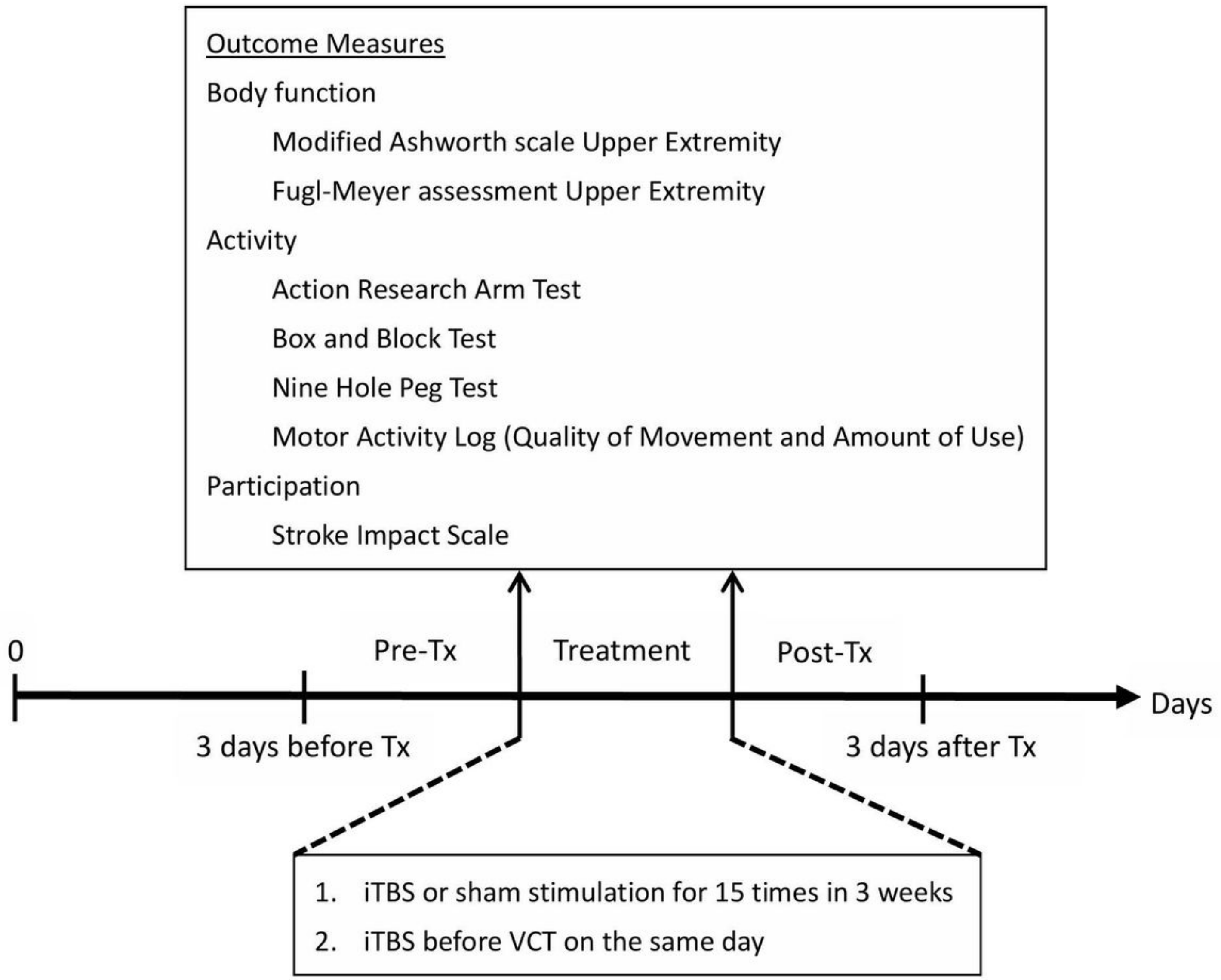

Figure 2

Experimental protocol

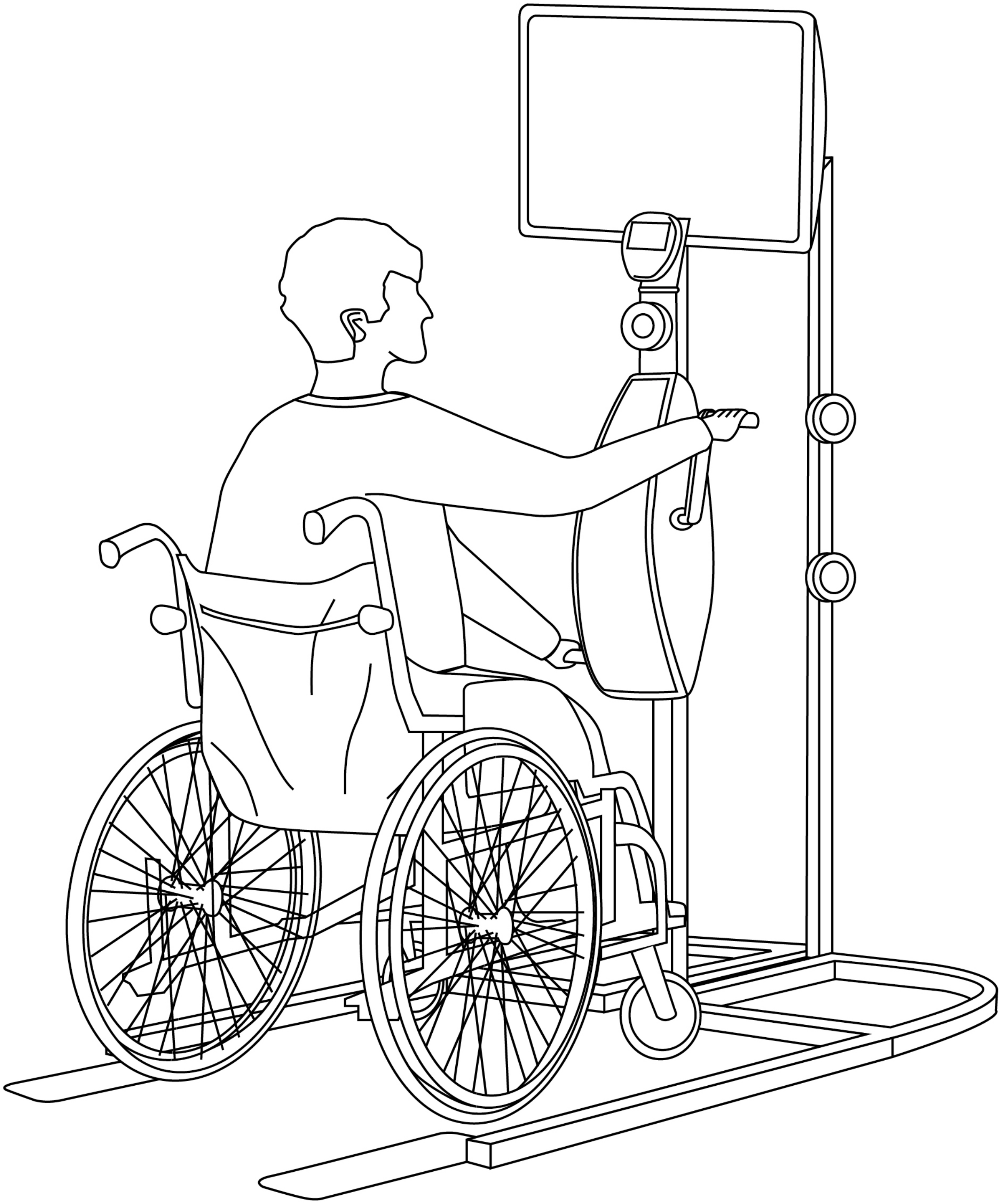

Figure 3

The setup of the VCT