Augmented Efficacy of Intermittent Theta Burst Stimulation on the Virtual Reality-based Cycling Training for Upper Limb Function in Patients With Stroke

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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, including Modified Ashworth Scale Upper Extremity (MAS-UE), Fugl-Meyer Assessment Upper Extremity (FMA-UE) for body function, Action Research Arm Test (ARAT), Nine Hole Peg Test (NHPT), Box and Block Test (BBT) and Motor Activity Log (MAL) for activity and Stroke Impact Scale (SIS) for participation were assessed before and after the intervention. 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, and with borderline significance in ARAT, BBT and MAL. There was no significant difference in FMA-UE between groups.

Conclusions: Intermittent TBS showed augmented efficacy on VCT for reducing spasticity, improving gross motor function and 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 that cause functional limitations. UL functional impairment commonly persists after the acute phase [1], resulting in long-term disability and decreased health-related life quality. Despite receiving traditional neurorehabilitation program, 50-60% of post-stroke patients remained variable degrees of functional motor limitations [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, virtual reality (VR), transcranial direct current stimulation, 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 virtual reality 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]. Taken together, this study applies virtual reality-based cycling training (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 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 impairments.

Theta burst stimulation (TBS) is a novel stimulation protocol of rTMS that requires a lower 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 changes in motor-evoked potential (MEP) [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]. Therefore, iTBS was administered over the primary motor cortex of the ipsilesional hemisphere to assess its efficacy for enhancing UL motor recovery.

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 [15], 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 [16]. 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. Outcome measures were body function, activities and participation of upper limb, with Modified Ashworth Scale Upper Extremity (MAS-UE), Fugl-Meyer Assessment Upper Extremity (FMA-UE), Action Research Arm Test (ARAT), Box and Block Test (BBT), Nine Hole Peg Test (NHPT), Motor Activity Log (MAL), and Stroke Impact Scale (SIS) adopted as measurement scales. We hypothesized that post-stroke patients completing a 15-day treatment program with iTBS and VCT would have better upper limb motor function than the patients receiving sham stimulation and VCT.

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, and (4) 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) 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 website (<https://www.randomizer.org/>). Figures 1 and 2 illustrate schematic overviews of the randomized allocation and experimental procedure, respectively. Each patient received the VCT program for 60 minutes associated with iTBS or sham stimulation on the same day for 15 consecutive working days. Patients were evaluated before and immediately 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 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 [17]. 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. The MEP was recorded by the coil which was placed tangentially to the skull, at a 45° angle to the midsagittal axis to generate posterior-anterior current flow at targeted area. True stimulation was applied over the identified motor hot spot at an intensity of 80% active motor threshold (AMT), defined as the minimum TMS intensity required to evoke MEPs ($\geq 200 \mu\text{V}$) in at least 5 of 10 successive trials from the slightly contracted (approximately 10-20% of maximal strength) FDI muscle. Stimulation was applied to the mirror site of the hot spot over the unaffected hemisphere if MEP could not be induced on the lesioned side. 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 [18]. The sham stimulation with intensity lower than 70% AMT has no effect on MEPs, as demonstrated by a previous study [19], 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 [18, 20, 21]. Patients with no measurable MEP were stimulated at 70% of RMT. 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-s train of bursts, containing three 50Hz pulses repeated at intervals of 200ms, and

repeated twice with a 10-min break for a total of 1200 pulses. 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) [22], 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.

The improvement of body function was measured by MAS and FMA. MAS, 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 [23, 24]. The affected finger flexor muscles, wrist and elbow were evaluated. These MAS scores were summed to represent the UL spasticity, with 1+ calculated as 1.5. FMA is a performance-based scale, particularly for patients with stroke, to assess sensorimotor function including motor function, joint function, sensation and balance [25]. 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) [26]. BBT is a functional test to measure unilateral gross manual dexterity [27], 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 [28], in which patients insert nine pegs into nine holes of the pegboard and then pick them up as quickly as possible. The outcome variable is the total time spent to complete the task, and less time needed indicates better dexterity. MAL was assessed to determine patients' real life functional performance involving the affected arm based on 14 daily activities [29], including amount of use and quality of movement.

SIS, a patient-reported questionnaire, was performed to evaluate participation in patients with stroke [30]. 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 applied to assess whether the iTBS group had greater therapeutic effect than the control group. 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 ($0.01 \leq \eta^2 < 0.059$) [31]. Statistical significance level was set at $p < 0.05$ (one-tailed) for all analyses [32].

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. All patients could tolerate the intervention without adverse effects throughout the study. Table 1 presents demographic and clinical characteristics of the 23 participants. No significant baseline between-group difference in demographic and clinical characteristics was observed.

Body function

Paired *t*-tests revealed significant improvement after the intervention in both groups in FMA (control: $p = 0.002$; iTBS: $p = 0.018$), while only the iTBS group showed significant improvement in MAS (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 with a large effect size ($p = 0.004$, $\eta^2=0.302$), but did not have significantly greater gains in FMA ($p = 0.203$, $\eta^2 = 0.035$) (Table 2).

Activity

After the intervention, the iTBS group showed significant improvement in GM and grip domains of ARAT, and improvement in pinch domain with borderline significance (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 the iTBS group had greater gains in the GM than the control group with borderline significance (GM: $p = 0.086$, $\eta^2 = 0.092$). However, the changes in other ARAT domains did not differ between two groups (grasp: $p = 0.139$, $\eta^2=0.059$; grip: $p = 0.153$, $\eta^2 = 0.053$; pinch: $p = 0.117$, $\eta^2=0.07$).

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 greater gains than the sham group with borderline significance ($p = 0.083$, $\eta^2=0.094$). 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 ($p = 0.045$, $\eta^2=0.137$).

In MAL, the iTBS group showed significant improvement after the intervention, and the sham group had improvement with borderline significance in MAL-AOU (control: MAL-AOU: $p = 0.079$, MAL-QOM: $p = 0.256$; iTBS: MAL-AOU: $p = 0.012$, MAL-QOM: $p = 0.019$). ANCOVA revealed between-group differences with borderline significance in the gains following the intervention in MAL (MAL-AOU: $p = 0.065$, $\eta^2=0.272$; MAL-QOM: $p = 0.054$, $\eta^2=0.124$).

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 ($p = 0.002$, $\eta^2=0.339$).

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, NHPT and SIS than sham stimulation, and made more progress with borderline significance in ARAT, BBT and MAL. However, the changes in FMA 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 despite hands mobility following stroke was hard to reclaim, this study demonstrated that iTBS had a promising additional benefit on VCT to enhance manual dexterity. 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 [20], 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 [33]. 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 [34, 35]. Therefore, facilitatory rTMS and iTBS had been applied to lower spasticity in patients with a number of neurologic disorders [20, 33, 36–41] 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, 42, 43], 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 [40, 44] such as γ -aminobutyric acid [45], glutamate [46] and dopamine [47]. The mechanism for the anti-spastic effect of iTBS remains unclear to date, and further neurophysiological studies are warranted to identify the underlying mechanism. Overall, iTBS showed augmented effect on VCT for reducing spasticity in stroke patients.

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, and with borderline significance in BBT. These results partially resembled those of some previous studies [20, 48, 49]. Talelli et al reported that 6 patients with chronic stroke had shorter simple reaction times of gripping tasks after iTBS than after sham stimulation [48]. 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 [49]. A more recent study by Chen *et al*/reported that iTBS significantly improved the performance in BBT in 22 patients with chronic stroke [20]. These variable findings may be owing to different patient characteristics, since inter-individual response variability following iTBS had been observed [50]. 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 [51]. 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 [52–54]. 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. Additionally, the iTBS and VCT group showed greater gains than the VCT alone group, with borderline significance, only in the gross motor domain. 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 [55]. 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 [20]. 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. Therefore, it is reasonable that patients in our studies had greater gains in the gross motor domain than in the fine domains of ARAT. In conclusion, our results suggest that iTBS may have augmented efficacy on VCT for improving gross motor recovery, and may show benefit on fine motor recovery.

In this study, MAL scores decreased without significance after the intervention in the VCT alone group. One explanation is that VCT trained both UL rather than emphasizing on the affected UL. Moreover, the learned non-use phenomenon may play an important role [56], because patients may not be aware of the residual motor function of the affected UL [57]. Furthermore, this study demonstrated that only the iTBS and VCT combined group showed significant improvement in MAL after the intervention, and that the difference in changes between the iTBS and sham stimulation on VCT had a moderate to large effect with borderline significance. 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 [49]. 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 [20]. Although iTBS and VCT alone had no improvement in MAL, combination of iTBS and VCT made progress in this study. One possible hypothesis is that adding iTBS on VCT may change the neural network in motor cortex, and further outweigh the learned non-use phenomenon. However, the mechanism underlying needs a further study to

identify. In conclusion, iTBS may have a beneficial effect 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 [58]. These variable findings may due to different protocols. To sum up, since this study found that iTBS can augment the effect of VCT on improving gross manual dexterity, reducing spasticity and increasing upper limb motor function, iTBS can also be reasonably considered to augment the effect of VCT on enhancing participation.

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 [59–61]. Conversely, arm cycling involves repetitive bilateral arm training and is able to improve upper limb motor function [62]. Our findings were partially consistent with previous studies [20, 63]. Hsu *et al* found that six patients with subacute ischemic stroke receiving iTBS had measurable improvement compared with the other six patients receiving sham stimulation [63]. Chen *et al* revealed that iTBS had significant effect on upper limb motor function measured by the FMA in patients with chronic stroke [20]. 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 [16]. 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 [50, 64]. 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 motor recovery.

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.

Conclusions

Applying iTBS over the ipsilesional hemisphere had augmented efficacy on VCT in reducing spasticity, improving gross motor function and 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 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; MASU-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.

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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.

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Tables

Table 1 Demographic and clinical characteristics

	sham iTBS + VCT	iTBS + VCT	<i>P</i> -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%)	
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%)	
Aphasia			0.64 ^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, NIHSS: National Institutes of Health

Stroke Scale

Table 2 Descriptive and inferential statistics and analysis of outcome measures

Variables	sham iTBS + VCT (paired <i>t</i> -tests)			iTBS + VCT (paired <i>t</i> -tests)			ANCOVA	
	Pre-Tx	Post-Tx	<i>P</i> value	Pre-Tx	Post-Tx	<i>P</i> value	<i>P</i> 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	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 ± 42.58	42.83 ± 43.39	0.019*	0.054	0.124
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

* $p < 0.05$; † $p < 0.01$

Figures

Figure 1

Flow diagram of recruitment and randomized allocation

Figure 2

Experimental protocol