Effectiveness of Repetitive Transcranial Magnetic Stimulation Combined with Visual Feedback Training in Improving Neuroplasticity and Lower Limb Function After Chronic Stroke

Hsien-Lin Cheng
Taipei Medical University Hospital

Chueh-Ho Lin
Taipei Medical University

Sung-Hui Tseng
Taipei Medical University

Chin-Wei Peng
Taipei Medical University

Chien-Hung Lai (chlai@tmu.edu.tw)
Taipei Medical University

Research Article

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Abstract

Background

After stroke, patients often experience lower limb motor deficits that interrupt their balance and gait functions and thereby lead to a high risk of falls. Sustained gait impairment can restrict participation in the activities listed in the International Classification of Functioning, Disability and Health model and poor quality of life. Repetitive transcranial magnetic stimulation (rTMS) and visual feedback training (VF) are key focuses in advanced rehabilitation medicine. The present study investigated the effectiveness of rTMS and VF training in improving lower limb motor performance, gait, and corticospinal excitability in patients with chronic stroke.

Methods

We recruited 30 patients with paretic legs at an average Brunnstrom stage of 3.7. The average time after the onset of stroke was 36.4 months. The patients were randomized into three groups: rTMS and VF, sham rTMS and VF, and sham rTMS and conventional rehabilitation groups. All participants underwent 50-minute intervention sessions three times per week for 4 weeks. The motor-evoked potential (MEP) of the tibialis anterior muscle, Berg Balance Scale (BBS) scores, Timed Up and Go (TUG) test scores, and Fugl–Meyer Assessment of Lower Extremity (FMA-LE) scores were determined before and after the intervention.

Results

The baseline characteristics were similar among the groups. After the intervention, the rTMS and VF group had improved MEP latency ($Z = -2.547, P = 0.011$), TUG scores ($Z = -2.666, P = 0.008$), and BBS scores ($Z = -2.539, P = 0.011$). The sham rTMS and VF group had improved MEP latency ($Z = -2.207, P = 0.027$) and TUG scores ($Z = -2.687, P = 0.052$). The sham rTMS and conventional rehabilitation group had improved TUG scores ($Z = -2.537, P = 0.066$).

Conclusions

rTMS and VF training may enhance the cortical excitability and walking ability of individuals with chronic stroke. However, future studies should use a larger study population and longer intervention time to validate this finding.

Trial registration:
This study was registered on the ClinicalTrials.gov Protocol Registration and Results System (ID:NCT03689491).

Background

After stroke, patients often experience lower limb motor deficits that interrupt their balance and gait functions, which leads to a higher risk of falls. Sustained gait impairment results in restricted participation in the activities listed in the International Classification of Functioning, Disability and Health (ICF) model and poor quality of life. Occupational therapy and physical therapy are the standard for stroke rehabilitation and motor recovery. Several researchers have developed new restorative therapies with a focus on neural activity in brain network dynamics. Motor recovery after stroke has been reported to be considerably influenced by the neuroplasticity of the brain motor network (1, 2). This reorganization of the brain continues throughout the patient’s life; it is particularly prominent in the acute phase after a brain lesion but can persist for years following a stroke (3, 4).

Numerous studies have reported that after stroke, interhemispheric competition becomes considerable (5–7); generally, enhanced contralesional excitability and increased interhemispheric inhibition occur. This state is associated with poorer function in the paretic limbs (8–10). Studies have demonstrated that cortical activity shifting from the contralesional to the ipsilesional motor area is associated with improved outcomes (9–12). These findings indicate that modulating cortical excitability to restore normal neural activity patterns is a potential strategy for stroke rehabilitation.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive therapeutic tool that can be used to modulate cortical excitability either directly through the application of facilitatory stimulation (high-frequency rTMS over the lesioned hemisphere) or indirectly through suppressive stimulation (low-frequency, inhibitory stimulation) to the contralesioned hemisphere (5, 6, 12). Studies have indicated that high-frequency rTMS or intermittent theta burst stimulation can modulate brain plasticity and thereby influence balance and walking functions (13, 14). Inhibitory (1-Hz) rTMS applied over the contralesional hemisphere is safe and involves hotspots that are easier to locate. This form of rTMS was reported to increase excitability within the ipsilesional hemisphere (15). Studies have demonstrated that 1-Hz rTMS improved walking functions and led to a more symmetrical gait pattern in patients after stroke (16, 17). In addition, a recovery of motor deficits was reported to be associated with reduced interhemispheric asymmetry in leg motor excitability (18). Although these results are preliminary, they support the application of rTMS over the leg region in patients with stroke.

Visual feedback (VF) training is a common approach to stroke rehabilitation. VF systems involve computer-based technology that provides feedback on performance. Patients with stroke can apply this feedback in repeating activities in training with increasing intensity. The repetition facilitates motor learning and neuroplasticity (19). Studies have demonstrated that VF training in tandem with visual, auditory, and proprioceptive feedback can effectively improve muscle activation, balance, and walking ability (20, 21) and is associated with an increase in activity in many regions within the visuomotor
network and the ipsilateral primary motor cortex (22–24). In our previous study, we proposed a novel ankle joint motion- and position-sensing measurement system that can be used to measure the range of motion and proprioception of the ankle (25). We incorporated this system into video game–based training programs in which patients with ankle inversion and eversion performed ankle dorsiflexion and plantarflexion in the sagittal and frontal planes (25). In other studies, VF gaming training was conducted in 12 to 18 sessions with intervention periods of 4 to 6 weeks (19, 26–28).

Although numerous studies have demonstrated that rTMS or VF training is effective in improving motor recovery after stroke, no study has combined rTMS and VF training of the lower limbs for stroke rehabilitation. The present study investigated the effects of combinations of rTMS and VF training, sham rTMS and VF training, and sham rTMS and conventional training on lower limb motor performance, gait function, and corticospinal excitability in patients with chronic stroke. We selected the tibialis anterior (TA) muscles as the targets for rTMS because they are crucial for ankle joint movement and are located in a focus region of our VF training system. We hypothesized that the patients receiving real rTMS plus VF training or sham rTMS plus VF training would exhibit greater improvement in their lower limb motor function, balance, and mobility and reduction in contralesional to ipsilesional interhemispheric inhibition than those receiving sham rTMS and conventional training would.

**Methods**

**Participants**

This study was approved by the Taipei Medical University Institutional Review Board (TMU-JIRB No.: N201607042). All participants provided written informed consent prior to participation. Patients with first-ever, chronic (> 6 month after stroke onset), or monohemispheric stroke (either infarction or haemorrhage) and who exhibited substantial leg impairment, as indicated by a Brunnstrom score above Ш, were enrolled in the study between 2017 and 2019. All participants were aged between 55 and 79 years and were able to walk independently for at least 10 m with or without assistive devices (e.g., cane or ankle-foot splint). The exclusion criteria were age over 80 years; a history of seizures or epilepsy; use of a pacemaker, aphasia, apraxia, concomitant neurological diseases or other severe medical diseases; and undetectable motor-evoked potential (MEP) of the TA muscle of the nonparetic leg.

**Study design**

The enrolled participants were blinded and randomized into three matched groups, which received 40 minutes of VF training (experimental group) or conventional training (control group) immediately after a 10-min session of either real or sham rTMS. The experimental group completed combination rTMS and VF training with either real (Group E1) or sham (Group E2) rTMS applied. The control group received sham rTMS and conventional rehabilitation (Group C; Fig. 1). The protocols of the interventions applied to the three groups are presented in Fig. 2. All participants received 50-minute treatment sessions three times per week over the course of 4 weeks. A well-trained and qualified occupational therapist delivered
the rTMS and VF or conventional training. Measurements were taken in a pretest (1 day before intervention) and a posttest (1 day after intervention) by a blinded examiner.

**Transcranial magnetic stimulation procedure**

Participants were seated comfortably, with a headrest to keep their heads stabilized and a leg rest to keep their knee flexed at 45° (Fig. 3A). The MEP of the TA muscle was induced through transcranial magnetic stimulation (TMS) by using a MagStim Rapid2 stimulator (MagStim, Carmarthenshire, UK) with a 70-mm figure-eight-coil placed over the contralateral motor cortex and equipped with a surface electromyography (EMG) recording system (Sierra Wave EMG/EP system using Ag-AgCl electrodes). An active electrode was placed on the TA muscle, and a reference electrode was placed on the inferior border of the patella. The optimal scalp position was determined by holding the coil tangentially over the leg area and moving in 5-mm steps every 5–8 s along the optimal site for receiving a response from the TA muscle. The motor threshold was defined as the minimal intensity required to evoke an MEP of greater than 50 μV in more than 5 out of 10 trials during activation (29). Hotspots were defined as the sites that yielded the strongest TA MEP. The location of the hotspot stimulation site of each hemisphere was marked and recorded to ensure consistency across sessions. The latency and amplitude of the MEP were measured in the pretests and posttests to identify changes in the corticospinal excitability. During each session, rTMS was performed using a 70-mm figure-eight coil at a 100% resting motor threshold and a train of 600 pulses (1 Hz) for 10 minutes over the leg area of the motor cortex on the unaffected hemisphere. Sham rTMS was performed with the coil held perpendicularly to the scalp and the same stimulus intensity and pattern.

**Individualized game-based VF intervention**

To enable provision of appropriate real-time VF training, we developed an individualized ankle haptic exercise program combined with a flying video game in which an airplane was controlled by the patients’ paretic ankle movements (25). In the individualized ankle haptic exercise training group, each participant sat in a comfortable chair facing the training table, on which an LCD screen was placed. The ankle haptic interface was placed under the table. The paretic ankle was positioned on the ankle haptic interface and Velcro was used to fix the paretic ankle’s position. The paretic leg was fixed using Velcro and lower extremity support to prevent abnormal compensation movements that might affect the paretic ankle VF training. The paretic joints were placed in a neutral starting and calibration position (Fig. 3B). The apparatus was custom made by Accu Balances Corporation (Taipei, Taiwan) and comprised an ankle haptic interface, two rotary potentiometers, and a lower extremity support. Data on the movement of the paretic ankle joint in the sagittal and frontal planes were collected by two rotary potentiometers and were transferred to a computer as input device data from a Logitech USB compact stick (942-000009; Logitech International S.A., Switzerland) during training. Each participant was asked to move their paretic ankle to the extent of its range in the sagittal and frontal planes. The researcher then recalibrated the range of the joystick device input in the Windows operating system for each participant on the basis of these movement data before the training commenced. This ensured that the full range of the game controls would be adjusted to match each patient’s movement limitations. When the patients participated in the
individualized game-based VF intervention, the movements of their paretic ankle controlled an aircraft in the flying video game, and this movement was displayed in real-time on the LCD monitor to provide the participants with direct VF.

**Conventional training**

The conventional training involved lower extremity, transfer, and balance strengthening and functional ambulation training and was individualized to suit the functional status of each patient.

**Outcome measurements**

**Motor performance**

The Berg Balance Scale (BBS) is used to objectively determine a patient's ability to safely balance as they perform a series of tasks (30). The BBS contains 14 items, each of which is rated on a 5-point ordinal scale ranging from 0 to 4, with 0 representing the lowest level of function and 4 representing the highest level of function. The Time Up and Go (TUG) test, which is used to measure dynamic balance and an individual's ability to perform advanced mobility tasks (31), was used to identify changes in the gait and balance of the study participants. If the patient was unable to complete the TUG test within 120 seconds, their time was recorded as 120 seconds. Neurological recovery of the lower limbs was assessed using the Fugl–Meyer Assessment of Lower Extremity (FMA-LE; 32). Each item was rated on a 3-point ordinal scale ranging from 0 (no performance) to 2 (complete performance), with a highest possible score of 34. The Fugl–Meyer Assessment is a feasible and efficient clinical examination that has been recommended for evaluating changes in motor impairment after stroke.

**Corticospinal excitability**

MEP has been demonstrated to be a sensitive measure for analyzing residual corticospinal functions and to be a predictor of motor recovery after stroke. In the present study, in the analysis of MEP, the optimal single TMS settings were adjusted to obtain the highest MEP. The stimulation intensity was set to 110% of the initial resting motor threshold. The highest MEP (hotspot) was determined, and the peak-to-peak MEP amplitudes and MEP latencies from 10 motor responses induced at an intensity of 110% of the initial resting motor threshold were averaged. If the TA muscles were unresponsive at the resting motor threshold, the MEP was recorded as undetectable.

**Data analysis**

We used SPSS software (version 19.0) for data analyses. The $\chi^2$ analysis was used to compare the categorical demographic variables. Change scores were calculated by subtracting pretest data from posttest data. All continuous variables (BBS scores, TUG scores, FMA-LE scores, MEP latency, MEP amplitude, and change) were tested using the Kruskal–Wallis test to identify intergroup differences in the baseline characteristics, pretest results, and posttest results. To investigate the effects of the intervention, we adopted the nonparametric Wilcoxon signed-rank test to identify intragroup differences in the pretest
and posttest scores. The nonparametric Mann–Whitney U test was used to compare the cortical excitability of the bilateral hemispheres. Significance was set as a 2-tailed \( P < 0.05 \).

### Results

#### Participants

This study enrolled 30 patients with first-ever, monohemispheric, or chronic stroke. No significant differences were identified in the baseline characteristics between the rTMS and VF, sham rTMS and VF, and sham rTMS and conventional rehabilitation groups (Table 1). The average time after the onset of stroke was 36.4 months, and the average Brunstrom stage of the paretic leg was 3.7, which indicated that the participants had chronic and profound lower limb motor deficits. None of the participants reported seizure induction, dizziness, or adverse events after the rTMS or sham stimulation.

![Table 1](attachment:participant_characteristics.csv)

<table>
<thead>
<tr>
<th></th>
<th>Group E1 (n = 10)</th>
<th>Group E2 (n = 10)</th>
<th>Group C (n = 10)</th>
<th>F ((\eta))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3 ± 15.3</td>
<td>56.4 ± 17.5</td>
<td>61.1 ± 13.2</td>
<td>0.406</td>
<td>0.670</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/4</td>
<td>6/4</td>
<td>7/3</td>
<td>(0.287)</td>
<td>0.866</td>
</tr>
<tr>
<td>Modified Ashworth Scale, MAS</td>
<td>0.8 ± 0.9</td>
<td>0.9 ± 0.8</td>
<td>1.2 ± 1.0</td>
<td>0.485</td>
<td>0.621</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>29.9 ± 0.3</td>
<td>30 ± 0.1</td>
<td>29.6 ± 0.9</td>
<td>1.258</td>
<td>0.300</td>
</tr>
<tr>
<td>Time poststroke, months</td>
<td>29.8 ± 20.9</td>
<td>31.6 ± 23.8</td>
<td>48.0 ± 29.0</td>
<td>1.635</td>
<td>0.214</td>
</tr>
<tr>
<td>Br. stage of lower extremity</td>
<td>3.8 ± 0.8</td>
<td>3.7 ± 0.5</td>
<td>3.5 ± 0.8</td>
<td>0.444</td>
<td>0.646</td>
</tr>
</tbody>
</table>

Br. stage, Brunnstrom stage.

Values are expressed as means ± standard deviations.

Intergroup differences were analyzed using Kruskal–Wallis test for continuous variables and \(\chi^2\) test for categorical variables.

\(*P < 0.05\)

#### Motor performance

The motor performance results and functional measurements are listed in Table 2. No significant intergroup differences were identified in the pretest and the posttest, with the exception of Group E1, which had significantly different BBS \((Z = -2.539, P = 0.011)\) and TUG \((Z = -2.666, P = 0.008)\) scores in the posttest.
## Table 2
Motor performance and functional measurements

<table>
<thead>
<tr>
<th></th>
<th>Pretest</th>
<th>Posttest</th>
<th>Change</th>
<th>( P^a ) for Intragroup Difference</th>
<th>( P^b ) for Intergroup Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fugl–Meyer Assessment of Lower Extremity (FMA-LE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>25.1 ± 9.2</td>
<td>25.6 ± 8.9</td>
<td>0.5 ± 0.8</td>
<td>0.102</td>
<td>0.441</td>
</tr>
<tr>
<td>Group E2</td>
<td>19.7 ± 8.7</td>
<td>20.6 ± 8.9</td>
<td>0.9 ± 2.1</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>24.9 ± 7.1</td>
<td>25.0 ± 7.0</td>
<td>0.1 ± 0.3</td>
<td>0.317</td>
<td></td>
</tr>
<tr>
<td><strong>Berg Balance Scale (BBS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>41.7 ± 11.5</td>
<td>43.6 ± 10.9</td>
<td>1.9 ± 1.5</td>
<td>0.011*</td>
<td>0.167</td>
</tr>
<tr>
<td>Group E2</td>
<td>34.7 ± 13.8</td>
<td>37.5 ± 14.9</td>
<td>2.8 ± 4.6</td>
<td>0.066</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>40.3 ± 18.2</td>
<td>41.4 ± 18.5</td>
<td>1.1 ± 2.5</td>
<td>0.109</td>
<td></td>
</tr>
<tr>
<td><strong>Time Up and Go (TUG)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>39.3 ± 32.2</td>
<td>29.8 ± 17.2</td>
<td>−9.4 ± 17.8</td>
<td>0.008*</td>
<td>0.052</td>
</tr>
<tr>
<td>Group E2</td>
<td>51.4 ± 40.2</td>
<td>49.1 ± 40.2</td>
<td>−2.2 ± 4.3</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>30.8 ± 23.9</td>
<td>30.5 ± 39.4</td>
<td>−0.2 ± 1.6</td>
<td>0.541</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviations.

\( P^a \) Wilcoxon signed-rank test.

\( P^b \) Kruskal–Wallis test.

\(*P < 0.05\)

## Corticospinal excitability

The corticospinal excitability results are presented in Table 3. The latency and amplitude of the MEP of the TA muscle on the affected side was undetectable in 11 patients during the pretest (4 in Group E1, 4 in Group E2, and 3 in Group C). No significant intergroup differences were noted in the pretest. After the intervention, we discovered that Group E1 exhibited significantly increased MEP latency in the TA muscle on the unaffected side (\( Z = −2.547, P = 0.011 \)) and increased MEP amplitude in the TA muscle of the affected side (\( X = −2.207, P = 0.027 \)). Group E1 also exhibited a significant intergroup difference (\( F = \)
4.438, $P = 0.006$), which indicated that the inhibitory rTMS over the unaffected hemisphere effectively modulated corticospinal excitability. Notably, in one patient in Group E1 who was determined to be unresponsive in the pretest, both MEP latency and amplitude were detected on the affected side in the posttest.
### Table 3
Cortical excitability

<table>
<thead>
<tr>
<th></th>
<th>Pretest</th>
<th>Posttest</th>
<th>Change</th>
<th>( p ) for Intragroup Difference</th>
<th>( p ) for Intergroup Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEP latency</strong>(^{\text{UH}}), ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>27.1 ± 1.9, n = 10</td>
<td>29.8 ± 3.1, n = 10</td>
<td>2.6 ± 3.5</td>
<td>0.011* (−2.547)</td>
<td>0.092</td>
</tr>
<tr>
<td>Group E2</td>
<td>27.9 ± 2.9, n = 10</td>
<td>28.1 ± 2.7, n = 10</td>
<td>0.2 ± 3.0</td>
<td>0.799 (−0.255)</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>27.1 ± 2.2, n = 10</td>
<td>28.4 ± 1.5, n = 10</td>
<td>1.2 ± 1.9</td>
<td>0.093 (−1.682)</td>
<td></td>
</tr>
<tr>
<td><strong>MEP amplitude</strong>(^{\text{UH}}), mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>0.9 ± 0.8, n = 10</td>
<td>0.7 ± 0.5, n = 10</td>
<td>−0.1 ± 0.3</td>
<td>0.205 (−1.268)</td>
<td>0.546</td>
</tr>
<tr>
<td>Group E2</td>
<td>1.0 ± 0.3, n = 10</td>
<td>1.0 ± 0.3, n = 10</td>
<td>0.02 ± 0.5</td>
<td>0.758 (−0.308)</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>1.1 ± 0.7, n = 10</td>
<td>1.3 ± 1.0, n = 10</td>
<td>0.1 ± 0.7</td>
<td>0.989 (−0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>MEP latency</strong>(^{\text{AH}}), ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>34.2 ± 3.5, n = 6</td>
<td>30.7 ± 4.1, n = 7</td>
<td>0.9 ± 12.8</td>
<td>0.116 (−1.572)</td>
<td>0.413</td>
</tr>
<tr>
<td>Group E2</td>
<td>32.9 ± 3.6, n = 6</td>
<td>32.8 ± 5.4, n = 6</td>
<td>−0.03 ± 4.8</td>
<td>0.917 (−0.105)</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>32.0 ± 3.0, n = 7</td>
<td>33.2 ± 4.1, n = 7</td>
<td>0.8 ± 3.9</td>
<td>0.674 (−0.420)</td>
<td></td>
</tr>
<tr>
<td><strong>MEP amplitude</strong>(^{\text{AH}}), mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group E1</td>
<td>0.5 ± 0.2, n = 6</td>
<td>1.0 ± 0.7, n = 7</td>
<td>0.3 ± 0.5</td>
<td>0.027* (−2.207)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Group E2</td>
<td>0.5 ± 0.2, n = 6</td>
<td>0.5 ± 0.5, n = 6</td>
<td>−0.03 ± 0.2</td>
<td>0.581 (−0.552)</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>0.5 ± 0.3, n = 7</td>
<td>0.4 ± 0.3, n = 7</td>
<td>−0.06 ± 0.2</td>
<td>0.343 (−0.948)</td>
<td></td>
</tr>
</tbody>
</table>
In the pretest, the interhemispheric differences in MEP latency were significant for all three groups (Group E1: \(Z = -3.256, P = 0.001\); Group E2: \(Z = -2.397, P = 0.017\); Group C: \(Z = -2.832, P = 0.005\); Fig. 4A), and the MEP amplitude was significant for Group C (\(Z = -2.664, P = 0.008\); Fig. 4B). After the intervention, the patients in Group E1 exhibited relatively symmetrical MEP latency between the bilateral hemispheres (\(Z = 0.537, P = 0.591\); Fig. 4C). No significant interhemispheric differences in MEP amplitude were noted for any of the three groups in the posttest although Group E1 exhibited a trend of improvement in the affected hemisphere (\(Z = -0.736, P = 0.462\); Fig. 4D).

**Discussion**

The present study investigated the effectiveness of contralesional rTMS combined with subsequent VF intervention in patients with chronic stroke. To the best of our knowledge, this is the first study to investigate the effectiveness of combining rTMS and VF training of the lower limbs for individuals with chronic stroke; previous studies have investigated whether rTMS or VF training could improve upper limb motor function or motor activity after stroke (33, 34). Our results reveal that none of the observed outcome variables differed significantly among the three groups. However, the group that completed the rTMS and VF training treatment exhibited within-group significant differences in their BBS scores, TUG scores, and MEP latencies and amplitudes. A study reported that BBS scores are the most accurate predictors of falls (35), and another reported that the TUG test, a dynamic balance measurement, can more accurately predict falls than static balance measurements can (36).

MEP, which can be generated through the application of TMS to the motor cortex, can be used to quantify corticospinal excitability during stimulation (37). In the current study, we discovered a significantly prolonged MEP latency and a trend of a decreasing MEP amplitude in the unaffected hemisphere in Group E1 (the rTMS and VF training group) that were not present in the other groups. Our results also reveal that Group E1 exhibited a significant increase in MEP amplitude in the affected hemisphere after intervention. These results indicate that the 1-Hz, low-frequency rTMS applied to the unaffected side of the brain inhibited corticospinal excitability in the unaffected hemisphere and enhanced corticospinal excitability in the affected hemisphere. The findings of this study support those of Wang et al. (18), whose data revealed that inhibitory (1-Hz) rTMS reduced MEP in the unaffected hemisphere and
consequently increased the MEP amplitude in the affected hemisphere. In addition, our results support the concept of interhemispheric competition because they indicate that the 1-Hz rTMS administered to the unaffected hemisphere reduced the interhemispheric inhibition of the affected hemisphere (38, 39).

The participants exhibited significant improvements in their BBS and TUG scores after they completed the rTMS and VF training. The BBS is a functional balance test that effectively represents an individual's ability to control their balance (30). The TUG has good reliability and is an effective indicator of impairments of the lower limbs, means of assessing functional mobility, and predictor of falling risk in stroke survivors (40). The findings of the present study indicate that rTMS can be used to induce neuroplastic changes and to promote motor function restoration.

VF training is often considered to be an effective approach to rehabilitation because it offers the following benefits. First, repetitive, intensive, and meaningful task-specific training promotes cortical reorganization and can be effective neurological rehabilitation treatment strategy. Second, VF training–enriched therapeutic environments improve patients’ focus on, motivation for, and adhesion to training tasks. Third, concurrent augmented feedback regarding performance re-establishes participants’ spatial awareness and abilities to plan their future actions. Fourth, participants in VF training often practice for longer periods because they receive positive feedback through goal achievement and scores (41, 42). In the present study, the airplane in the video game was controlled by ankle movement because ankle movement is crucial in the recovery process of stroke survivors. Studies have reported that ankle and foot abnormalities can have subsequent effects on the knee and hip joints as well as on gait patterns (43, 44). This airplane game VF training encouraged dorsiflexion, plantarflexion, inversion, and eversion of the ankle. Being able to view how the ankle movement controlled the airplane movement on the screen provided the stroke survivors with positive feedback and encouragement.

In the present study, both the VF training and conventional training groups exhibited improvement in their FMA-LE, BBS, and TUG scores and in their corticospinal excitability after the interventions. However, no significant intragroup or intergroup differences were identified in the FMA-LE, BBS, and TUG scores or in the corticospinal excitability of the VF training and conventional training groups. These findings are compatible with those of other studies, which have reported results that demonstrated that virtual reality or interactive video game exercises had similar effects to those of conventional rehabilitation on upper limb function, gait speed, balance, participation, and quality of life (28, 45).

This pilot study has several limitations, including a small sample size and short intervention duration, which precluded long-term evaluation. In addition, a figure-eight coil was used to apply the stimulator to the site. Nondetectable MEP was recorded for 11 of the 30 included patients; a cone coil may be able to more easily induce MEP and to achieve more effective therapy. Nevertheless, the rTMS treatment of this study was demonstrated to positively affect the participants’ BBS scores, TUG scores, and corticospinal excitability. Other studies using the same parameters and coils as those used in this study have also reported that rTMS treatment improved leg impairment, mobility, and corticospinal excitability in stroke survivors (17, 18).
Conclusions

The present study revealed that combined rTMS and VF training of the paretic ankle may modulate corticospinal excitability and subsequently potentially improve balance and functional mobility in individuals with chronic stroke. However, the pilot results of this study should be further validated in future studies with larger sample sizes or longer clinical trials.

Abbreviations

ICF: International Classification of Functioning, Disability and Health
rTMS: repetitive transcranial magnetic stimulation
VF: visual feedback
TA: tibialis anterior
MEP: motor-evoked potential
EMG: electromyography
BBS: Berg Balance Scale
TUG: Timed Up and Go Test
FMA-LE: Fugl–Meyer Assessment of Lower Extremity

Declarations

Ethics approval and consent to participate

All participants provided informed consent to participate in this study, and the study was approved by the Taipei Medical University Institutional Review Board (TMU-JIRB No.: N201607042).

Consent for publication

Not applicable.

Availability of data and materials

The data sets used and analyzed in the current study are available upon reasonable request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.
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Authors’ contributions

Cheng contributed to the conceptualization and designing of this study, was involved in the data acquisition and interpretation, and drafted the manuscript. Lin contributed to the conceptualization of the study and provided expertise on benchmarking, Tseng and Peng involved in the data collection and interpretation. Lai contributed to the designing of the study, drafted the manuscript, and revised the manuscript. All authors have read and approved the final manuscript.

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References


39. Takeuchi N, Tada T, Toshima M, Chuma T, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and


Figures
Figure 1. Enrollment flowchart.

Eligibility: n = 55
Patients with first-ever, chronic (>6 month after stroke onset),
or monohemispheric stroke (either infarction or
hemorrhaged), substantial leg impairment, and Brunstrom
stage above III between 2017 and 2019

Exclusion: n = 25
Age > 80 years,
history of seizures or epilepsy,
use of a pacemaker,
aphasia or apraxia,
concomitant diseases, and
undetectable MEP in the TA muscle
of the nonparetic leg

Enrolment
N = 30

Randomization

Assessments 1 day before
intervention
Motor performance
Corticospinal excitability

Group E1
n = 10
real rTMS +
VF training

Group E2
n = 10
sham rTMS +
VF training

Group C
n = 10
sham rTMS +
conventional
rehabilitation

Assessments 1 day after intervention
Motor performance
Corticospinal excitability

Figure 1
Enrollment flowchart.
Figure 2. Study design.
Figure 3

(A) Application of 1-Hz, 100% rTMS or sham rTMS before visual feedback training or conventional rehabilitation.

(B) Architecture of game-based visual feedback intervention system; movement at the extent of the paretic ankle's range in the sagittal (plantarflexion/dorsiflexion) and frontal (eversion/inversion) planes used to move an aircraft displayed in real time on an LCD monitor to provide direct visual feedback.
Figure 4

MEP latencies and amplitudes of unaffected and affected hemispheres.

(A) MEP latencies of unaffected and affected hemispheres in pretest.

(B) MEP amplitudes of unaffected and affected hemispheres in pretest.

(C) MEP latencies of unaffected and affected hemispheres in posttest.

(D) MEP amplitudes of unaffected and affected hemispheres in posttest.

Error bars represent the standard deviation of the mean.

*P < 0.05, **P < 0.01