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High-frequency repetitive transcranial magnetic stimulation enhanced treadmill training effects on gait performance in individuals with chronic stroke: A double-blinded randomized controlled pilot trial

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) combined with treadmill training has been suggested to modulate corticomotor activity and improve gait performance in people with Parkinson's disease.
Research question: It is unclear whether this combination therapy has a similar effect in people with stroke. The current study aimed to investigate whether high-frequency rTMS enhances the effects of subsequent treadmill training in individuals with chronic stroke.
Methods: Fourteen participants meeting the selection criteria were randomly assigned to either the experimental (n = 8) or control (n = 6) group. The experimental group received 5 Hz rTMS prior to treadmill training three times per week for 3 weeks. The control group received sham rTMS before treadmill training. Walking speed, gait symmetry, corticomotor excitability, motor function of the lower extremities, and muscle activity during walking were measured before intervention, after intervention, and at 1-month follow-up.
Results: The walking speed, spatial asymmetry of gait, and motor function of the lower extremities improved significantly in the experimental group, and these improvements exhibited significant differences in between-group comparisons. However, there was no significant difference in corticomotor excitability or brain asymmetry ratio after the intervention in each group.
Significance: The current results revealed that applying 5 Hz high-frequency rTMS over the leg motor cortex in the affected hemisphere enhanced the effects of subsequent treadmill training on gait speed and spatial asymmetry in individuals with chronic stroke. Improvement in gait speed persisted for at least 1 month in individuals with chronic stroke.

1. Introduction

Individuals suffering from stroke often exhibit poor motor control ability and impaired gait, including slow speed and gait asymmetry, even at the chronic stage [1,2]. Walking speed is related to activity level, and symmetry of gait is related to efficient walking performance [3,4]. Asymmetrical gait involves greater energy consumption and increased loading on the joints of the lower extremities [5,6].

Macko and colleagues [7] reported that walking distance and speed in individuals with stroke improved significantly after 6 months of treadmill training. Patterson and colleagues [8] demonstrated that walking speed, step length, and cadence improved significantly after 6 months of treadmill training. These results suggest that treadmill training is beneficial for restoring walking ability in people with stroke. Various mechanisms have been proposed for these beneficial effects. Some studies suggested that increasing neuronal activity in frontal, parietal, and temporal lobes after treadmill training improve walking speed [9,10]. Other studies suggested the involvement of reorganization of primary motor cortex, indicated by corticomotor excitability and mapping size [11,12].

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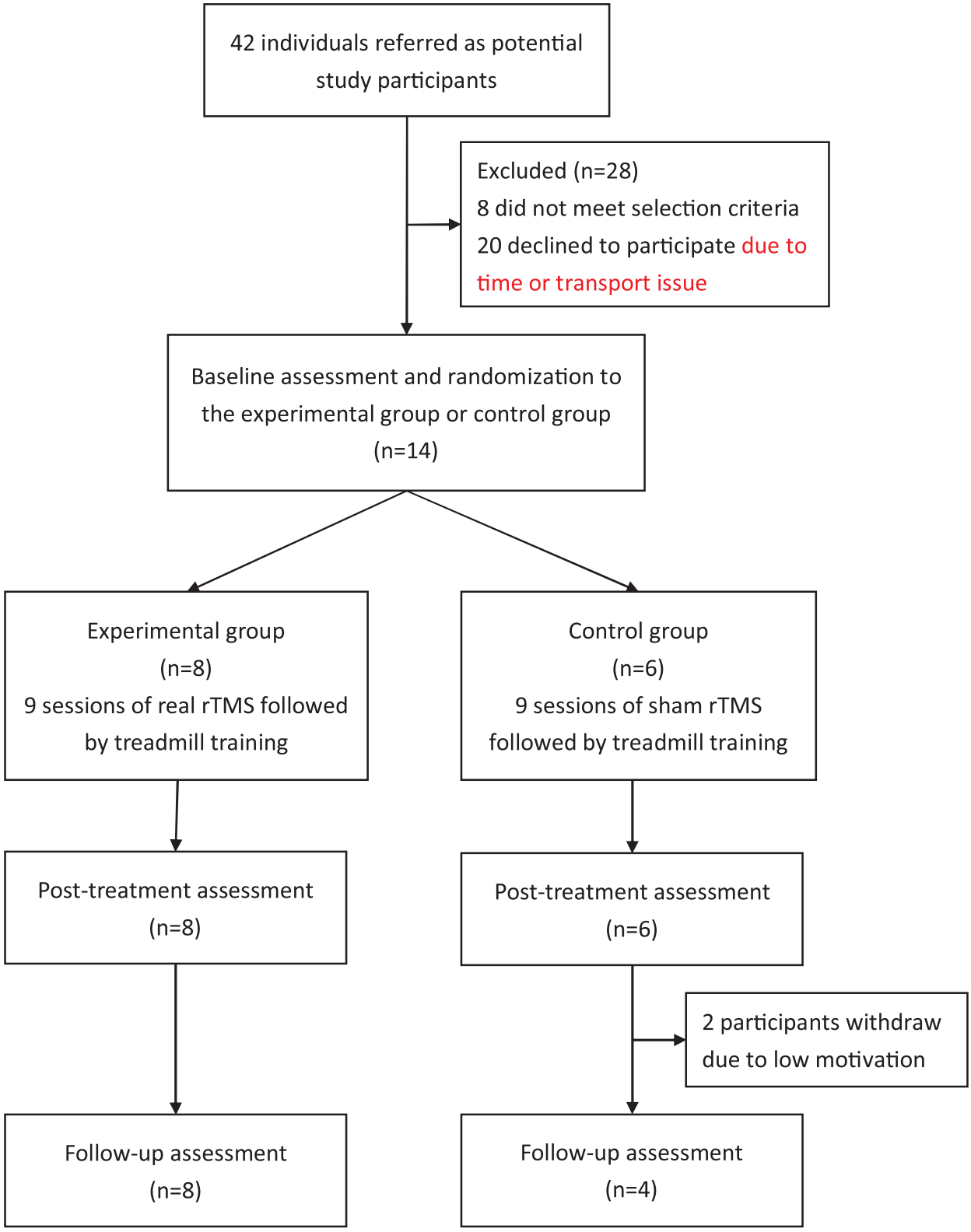

Fig. 1. Flow chart of the experimental design.
Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

Nowak et al. [13] reported that bilateral hemispheres are reciprocally inhibited to control normal functions. Interhemispheric balance is disturbed after stroke, leading to further inhibition of the affected hemisphere and thus poor motor control and functioning [13,14]. Repetitive transcranial magnetic stimulation (rTMS) can be used to modulate brain activity using stimulation of different frequencies [15]. High-frequency rTMS (≥ 5 Hz) causes a transient increase in cortical excitability, whereas low-frequency rTMS (1 Hz) decreases cortical excitability [15]. Kakuta et al. [15] reported that walking velocity was significantly higher for 20 min after stimulation of

Table 1
Baseline demographic and clinical characteristics of participants.

Variables	Experimental group (n = 8)	Control group (n = 6)	*p* value
Age (years)	53.5 ± 13.7	54.7 ± 12.2	0.651
Gender (male/female)	7/1	4/2	0.538
Affected hemisphere (left/right)	2/6	4/2	0.227
Type of stroke (hemorrhagic/ischemic)	3/5	5/1	0.138
Time poststroke (months)	31.8 ± 24.0	25.3 ± 15.7	0.746
Frequency of physical therapy (times/week)	2.4 ± 1.7	3.0 ± 1.8	0.424

Values are mean ± standard deviation or frequency.

the leg motor area with 10 Hz rTMS, compared with sham rTMS, in post-stroke patients. Chieffo et al. [15] demonstrated that 11 sessions of 20 Hz rTMS over the cortical motor area representing lower limbs in a 3-week period induced improved lower limb motor function in chronic stroke patients. Sasaki et al. [15] reported that application of 10 Hz rTMS over the leg motor areas was beneficial for patients with stroke, significantly improving lower limb function after rTMS. However, few studies have examined whether rTMS enhances exercise training effects, such as treadmill training, to maximize functional recovery in a short period of time. We previously demonstrated that 5 Hz rTMS, the lowest excitatory frequency, enhanced the effects of subsequent treadmill training on gait performance by modulating corticomotor excitability in people with Parkinson's disease [15]. However, the effects of rTMS on treadmill training have not been examined in people with stroke. We investigated the effects of 5 Hz rTMS followed by treadmill training on gait and cortical excitability in individuals with chronic stroke. We hypothesized that rTMS would enhance the effects of treadmill training on gait speed and symmetry, possibly owing to increased corticomotor excitability of the affected hemisphere.

2. Methods

2.1. Study design

We conducted a double-blinded (assessor and participants), randomized (blocks of four) controlled trial. Participants in the experimental and control groups received real and sham rTMS, respectively, followed by treadmill training, three times per week for 3 weeks. Outcomes were measured before intervention (pre), after completing a 9-session training period (post), and at 1-month follow-up. All participants received regular physical therapy during the study period. The experimental procedures were approved by the Institutional Review Board of Taipei Veterans General Hospital. The trial was registered at http://www.anzctr.org.au/ (ACTRN12617000717358).

2.2. Participants

Fourteen participants were enrolled. Inclusion criteria were: (1) diagnosis of unilateral hemiparesis secondary to stroke; (2) post-stroke time longer than 6 months; (3) able to walk independently with or without devices; and (4) a score of ≥24 on the mini-mental state examination. Exclusion criteria were: (1) metal implants in the brain; (2) unstable medical conditions; and (3) history of other diseases known to interfere with study participation.

2.3. Intervention

2.3.1. Repetitive transcranial magnetic stimulation

5 Hz rTMS was delivered to the motor hot spot of the tibialis anterior (TA) of the affected hemisphere by MagStim Rapid stimulation with a figure-of-eight coil (MagStim Rapid, MagStim Co., Ltd., Carmarthenshire, Wales, UK). The hot spot was defined as the lowest stimulus intensity necessary to elicit motor evoked potentials (MEPs) greater than 0.05 mV peak-to-peak amplitude in at least three of five consecutive stimuli, determined by moving the TMS stimulator over the scalp in 1-cm steps [16]. Devanne et al. [17] suggested that the optimal position of TA activation is achieved by placing the coil parallel to and approximately 0.5–1.0 cm lateral to the midline, with its mid-point aligned antero–posteriorly against the vertex (Cz). The real rTMS group received rTMS with an intensity of 90% of the resting motor threshold in a train of 900 pulses (5 Hz) for 15 min during each session. The train duration was 12 s with a 48-second intertrain interval, delivered while participants were at rest. Sham rTMS was delivered with the coil angle rotated 90° and only one wing of the coil touching the scalp of the participant to avoid inducing real stimulation. The parameters, including noise, time, and frequency of the sham rTMS, were the same as those of the real rTMS [15].

2.3.2. Treadmill training

Participants walked on a motorized treadmill (Biodex, Shirley, New York) with a safely harness immediately after real or sham rTMS, for 30 min each session. This training was outside of routine physical therapy session. Walking speed began at 50% of participants' comfortable over-ground walking speed for 5 min as a warm-up, and increased gradually for the remaining period, according to participants' tolerance. Tolerance was defined as participants' reporting perceived exertion of "somewhat hard" or lower (Borg rating of perceived exertion < 13). Treadmill training was conducted by the same physical therapist for all participants. The therapist observed participants' gait patterns and provided verbal feedback to encourage large symmetrical steps during training.

Table 2
Gait performance results for each group.

Variables	Experimental group			Control group		
	Pre	Post	Follow-up	Pre	Post	Follow-up
Speed (cm/s)	63.24 ± 34.31	75.87 ± 32.51*	83.36 ± 31.55*	57.87 ± 26.98	57.98 ± 25.86	59.23 ± 27.86
Change values [a] (%)		29.5 ± 23.9	46.9 ± 42.9		0.3 ± 6.6††	2.1 ± 7.5††
Spatial asymmetry ratio	0.18 ± 0.17	0.08 ± 0.13*	0.12 ± 0.08	0.19 ± 0.09	0.22 ± 0.17	0.17 ± 0.08
Change values [a] (%)		−57.0 ± 40.4	−1.7 ± 47.3		34.8 ± 97.1†	14.0 ± 92.9
Temporal asymmetry ratio	0.35 ± 0.17	0.29 ± 0.12	0.33 ± 0.14	0.35 ± 0.11	0.34 ± 0.14	0.35 ± 0.10
Change values [a] (%)		−11.9 ± 36.3	-1.5 ± 27.8		-3.1 ± 23.0	7.8 ± 32.4

*, ** $p <$ 0.025, 0.01 vs. pre; †, †† $p <$ 0.05, 0.01 vs. experimental group.
[a] Change values (%) were calculated by subtracting the baseline data from the post-training data (post) divided by baseline data or by subtracting the baseline data from the follow-up data (follow-up) divided by baseline data.

Table 3
Results of brain asymmetry ratio for each group.

	Experimental group			Control group		
	Pre	Post	Follow-up	Pre	Post	Follow-up
Motor evoked potentials (μV)	41.02 ± 25.89	55.73 ± 28.43	66.11 ± 61.11	54.12 ± 31.48	62.53 ± 52.43	65.80 ± 57.06
Affected hemisphere	195.77 ± 43.37	49.4 ± 56.6	59.6 ± 129.0	332.54 ± 163.85	5.3 ± 35.0	9.5 ± 41.0
Change values [a] (%)	0.67 ± 0.14	209.58 ± 93.17	222.10 ± 141.08	0.73 ± 0.03	320.01 ± 108.06	387.92 ± 486.94
Non-affected hemisphere		4.5 ± 32.5	22.9 ± 94.4		0.4 ± 17.0	60.2 ± 67.5
Change values [a] (%)		0.56 ± 0.18	0.59 ± 0.18		0.70 ± 0.15	0.81 ± 0.01
Brain asymmetry ratio						
Change values [a] (%)		−13.5 ± 31.3	−12.6 ± 11.0		−3.4 ± 17.2	10.6 ± 2.5

[a] Change values (%) were calculated by subtracting the baseline data (pre) from the post-training data (post) divided by baseline data or by subtracting the baseline data from the follow-up data (follow-up) divided by baseline data.

Table 4
Results of electromyography of affected TA and RF muscles for each group.

	Experimental group			Control group		
	Pre	Post	Follow-up	Pre	Post	Follow-up
Affected TA (μV)	15.18 ± 2.87	18.70 ± 5.55	18.22 ± 4.54*	17.99 ± 2.98	18.40 ± 5.56	17.13 ± 6.88
Change values [a] (%)		22.9 ± 25.8	19.2 ± 11.0		1.6 ± 20.9	-6.8 ± 25.2†
Affected RF (μV)	5.82 ± 2.54	7.68 ± 3.20*	6.50 ± 2.59	9.35 ± 2.38	9.36 ± 3.17	9.76 ± 3.58
Change values [a] (%)		35.9 ± 36.4	15.3 ± 18.3		-0.8 ± 14.0†	2.7 ± 17.2

Abbreviations: TA: anterior tibialis; RF: rectus femoris.
[a] Change values (%) were calculated by subtracting the baseline data (pre) from the post-training data (post) divided by baseline data or by subtracting the baseline data from the follow-up data (follow-up) divided by baseline data.
* $p < 0.025$ vs. pre.
† $p < 0.05$ vs. experimental group.

Table 5
Results of Fugl-Meyer assessment scale for each group.

	Experimental group			Control group		
	Pre	Post	Follow-up	Pre	Post	Follow-up
Fugl-Meyer score	26.6 ± 3.5	27.8 ± 3.5*	27.6 ± 3.4	26.8 ± 2.7	26.6 ± 3.6	26.8 ± 3.7
Change values [a] (%)		4.3 ± 2.6	4.0 ± 4.0		0.5 ± 3.3†	-0.2 ± 4.6

[a] Change values (%) were calculated by subtracting the baseline data from the post-training data (post) divided by baseline data or by subtracting the baseline data from the follow-up data (follow-up) divided by baseline data.
* $p < 0.025$ vs. pre.
† $p < 0.05$ vs. experimental group.

2.4. Outcome measures

2.4.1. Gait performance

Walking speed, spatial asymmetry and temporal asymmetry were measured using the GAITRite system (CIR system Inc., USA), comprising a straight walkway with pressure-sensitive sensors. The concurrent validity and reliability of this system have been established [18]. Participants were asked to walk on the walkway for three trials at a comfortable speed. The average speed was used for data analysis. The spatial asymmetry ratio was calculated as: $\left|1 - [\text{step length (affected)} \div \text{step length (unaffected limb)}]\right|$. The temporal asymmetry ratio was calculated as: $\left|1 - [\text{single support time (affected)} \div \text{single support time (unaffected)}]\right|$ [1,2]. Decrease in asymmetry ratio indicates improvement in gait symmetry.

2.4.2. Corticomotor excitability

MEPs of bilateral TA induced by TMS (MagStim 200, MagStim Co., Ltd., Carmarthenshire, Wales, UK) were recorded with electromyography (EMG) (BIOPAC System Inc., Goleta, CA, USA). Surface recording electrodes were placed over the TA muscle belly at 1/3 of the distance from the tibial tuberosity to the inter-malleolus line [19]. EMG signal sensitivity was set at 0.1 mV/div with a band-pass filter of 20 to 3000 Hz. The double cone coil of the TMS device was placed over the motor hot spot of the TA in the affected hemisphere to detect the resting motor threshold (MT). The MT was determined at rest as the minimum percentage of the stimulation output that induced MEPs greater than 0.05 mV peak-to-peak amplitude in at least three out of five trials over the motor cortex. MEPs were then recorded by applying 120% of MT five times. The average MEP was used as a measure of corticomotor activity. MEPs of the non-affected hemisphere were then recorded in the affected hemisphere using the same protocol. The brain asymmetry ratio was indicated using the following formula: $\left|[\text{MEP (affected)} - \text{MEP (unaffected)}] \div [\text{MEP (affected)} + \text{MEP (unaffected)}]\right|$ [20]. Smaller values indicate greater brain symmetry.

2.4.3. Muscle activity during walking

EMG of the TA and rectus femoris (RF) of the affected leg during walking were measured using Ag-AgCl surface electrodes. The active electrode for TA was placed on 1/3 of the distance from the tibial tuberosity to the inter-malleolus line. The RF electrode was placed on the midpoint between the anterior superior iliac spine and patella. The reference electrode was placed on the ulnar tuberosity. To determine the gait cycle, two footswitch sensors were placed under the heel and first metatarsal head. All signals were collected using the BIOPAC MP 150WMW system (BIOPAC System Inc., Goleta, CA, USA). The sampling

rate was 3000 Hz with a band-pass filter of 40 to 400 Hz and a low-pass filter of 60 Hz. After rectification, the signal was smoothed by another low-pass filter (9 Hz). The EMG signal of TA was calculated during the swing phase, while the EMG signal of RF was calculated during the stance phase of gait.

2.4.4. Motor control of the lower extremities

Lower extremity motor control was evaluated using the Fugl-Meyer assessment (FMA) scale which is reported to have good reliability for stroke patients [21]. The maximum total score is 34. Higher scores indicate better control of the lower extremities.

2.5. Statistical analysis

SPSS 20.0 (IBM Corp, Armonk, NY, USA) was used for analysis. Continuous variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test. To analyze intergroup differences, change values (%) were analyzed with the Mann-Whitney U test. Change values (%) were calculated by subtracting the baseline data from the post-training data, divided by the baseline data (post), or by subtracting baseline data from follow-up data, divided by baseline data (follow-up). The significance level was set at $p < 0.05$. The Friedman test with the post hoc Wilcoxon signed rank test were used for within-group comparisons. A Bonferroni adjustment was applied, resulting in a significance level set at $p < 0.025$.

3. Results

3.1. Participants

Fourteen participants completed the pre-test, nine sessions of training, and the post-test. However, two participants in the control group missed the 1-month follow-up assessment (Fig. 1). No participants reported any adverse events. The demographic characteristics and clinical features of participants in both groups were not significantly different between groups (Table 1). The treadmill speed in the experimental group was 2.89 ± 1.45 km/hour in the 1 st training session and increased to 3.64 ± 1.37 km/hour in the 9th training session ($p = 0.012$). The treadmill speed of control group was 2.52 ± 0.88 km/hour in the 1 st training session and increased to 3.20 ± 0.89 km/hour in the 9th training session ($p = 0.026$). There was no significant group difference in the increase of treadmill training speed ($p = 0.296$).

3.2. Gait parameters

Within-group comparisons revealed significant improvements in walking speed and spatial asymmetry in the experimental group after training (walking speed, $p < 0.025$; spatial asymmetry, $p < 0.025$) (Table 2). Walking speed in the experimental group improved significantly at follow-up compared with pre-test ($p < 0.025$). There were no significant changes in the control group in these gait parameters. Improvements in gait speed after training and at follow-up in the experimental group were significantly greater than in the control group ($p < 0.01$, effect size = 0.79; $p < 0.01$, effect size = 0.83, respectively). The experimental group exhibited a greater improvement in gait spatial asymmetry compared with the control group at post-test ($p < 0.05$, effect size = 0.59).

3.3. Corticomotor excitability

There were no significant within-group changes and between-group differences in MEPs of the affected and non-affected hemisphere and brain asymmetry ratio after training and at follow-up (Table 3).

3.4. Electromyography of the lower extremities during walking

EMG activity in the RF during the stance phase increased more in the experimental group after intervention ($p < 0.025$). A near-significant trend for an increase in the TA activity during the swing phase ($p = 0.05$) was observed after intervention. This increase was maintained at follow-up ($p < 0.025$). There were no significant changes in TA and RF EMG activity in the control group. Between-group comparisons revealed a significant improvement of TA activity at follow-up ($p < 0.05$) and RF activity at post-test ($p < 0.05$) in the experimental group compared with the control group (Table 4).

3.5. Motor control of the lower extremities

Within-group comparisons indicated that FMA scores in the experimental group were significantly improved after intervention ($p < 0.025$) compared with pre-test performance. FMA scores in the control group showed no significant changes at post-test or follow-up. Improvement in FMA scores at post-test was significantly greater in the intervention than control group ($p < 0.05$) (Table 5).

4. Discussion

The results revealed significant improvements in gait speed and spatial asymmetry after nine sessions of 5 Hz rTMS over the primary motor cortex of leg area prior to treadmill training in individuals with chronic stroke. Moreover, the gait speed improvement was retained at 1-month followed-up. We previously reported non-significant improvements in gait after 4 weeks of treadmill training in chronic stroke subjects [22]. In the current study, a non-significant improvement was also shown in the control group (receiving sham stimulation prior to treadmill training). A previous study suggested that brain plasticity along with functional improvement occurs in chronic stroke patients, but is not easily induced [23]. Cortical excitability has been reported to be transiently enhanced by 5 Hz rTMS applied to primary motor cortex [24]. Therefore, the 5 Hz high-frequency rTMS used in the current study may have exerted a modulatory effect on subsequent treadmill training, improving gait performance.

Macko et al. [7] and Patterson et al. [8] reported that the walking speed of chronic stroke subjects improved by approximately 18% and 22%, respectively, after 72 sessions of treadmill training over 6 months. However, the present results indicated that only nine sessions of treadmill training over 3 weeks improved walking speed by 29.5% if 5 Hz rTMS was applied before treadmill training. The duration post-stroke and walking speed at baseline of our participants were similar to those reported by Macko et al. and Patterson et al. Therefore, the current findings indicate that 5 Hz rTMS enhances the effects of subsequent treadmill training, shortening the training period. The present findings suggest that a beneficial effect on gait speed can be maintained or even improved at 1-month follow-up. However, the enhancing effect was not only achieved by high-frequency rTMS, but also by low-frequency rTMS, as reported in our previous study, which demonstrated that 1 Hz rTMS applied to the non-affected hemisphere primed task-oriented training in subjects with chronic stroke [25]. These findings indicate that rTMS of 1 Hz over the non-affected hemisphere and 5 Hz over the affected hemisphere both enhanced the training effects of subsequent intervention on gait performance.

Gait symmetry is another important parameter for energy consumption and loading on the lower extremity joints [26]. A previous study reported that gait symmetry was not improved after 72 sessions of treadmill training, possibly owing to task repetition reinforcing asymmetry on the treadmill [9]. However, in the present study, spatial asymmetry was improved after receiving rTMS and treadmill training. We speculate that the non-significant increase in cortical excitability by 5 Hz rTMS may have reflected a better environment for motor learning during treadmill training, resulting in better gait symmetry. Previous

studies have suggested that spatial asymmetry is related to poor motor control of the affected lower extremities and slow walking speed [2,27]. Improvements in the motor control of the affected leg, indicated by increased FMA scores and improvements in walking speed in the experimental group, may partially explain the improved spatial asymmetry in the present study. Furthermore, the increase in TA activity during the swing phase and RF activity during the stance phase observed in the present study may also contribute to improvements in gait symmetry after rTMS and treadmill training. The current results revealed that increases in EMG amplitude in these muscles were positively correlated with increased MEPs in the affected hemisphere (TA: $r = 0.981$, $p < 0.01$; RF: $r = 0.797$, $p < 0.05$). This suggests that improved spatial symmetry may derive from improved neuromuscular control. Accordingly, applying rTMS prior to treadmill training might result in better motor performance than treadmill training alone, indicated by our gait parameters, except temporal asymmetry. Lin et al. [2] reported that temporal asymmetry was determined by dorsiflexor muscle strength and ankle joint position sense, which were not measured in the present study. However, different training strategies, including emphasizing muscle strength or proprioception training, could be adopted to improve temporal asymmetry.

In the present study, corticomotor excitability was determined by examining MEPs induced by TMS. Although MEPs of the affected hemisphere increased and brain asymmetry ratio decreased accordingly in the experimental group, these changes were not significant. However, we found that MEP increases in the affected hemisphere after training were negatively correlated with brain asymmetry ratio ($r = -0.893$, $p < 0.05$). We previously reported significantly increased MEP amplitude in the affected hemisphere resulting in improved brain symmetry after applying 1 Hz rTMS to the non-affected hemisphere with task-oriented training, supporting the concept of interhemispheric inhibition [25]. Taken together with the present results, these findings suggest that the non-affected hemisphere may be modulated by low-frequency rTMS more easily than the affected hemisphere is modulated by high-frequency rTMS. In addition to rTMS frequency and hemisphere modulation, the total number of pulses delivered in each session, total number of sessions, and subsequent exercise training protocols may also have modulatory effects [24].

The current study involved several limitations, including a small sample size, and a small amount of 1-month follow-up data. However, effect sizes (0.59-0.83) were relatively large for gait speed and spatial asymmetry. A larger randomized controlled trial needed to validate the benefits and maintenance of the effects of 5 Hz rTMS and treadmill training shown in the current study. Finally, although the present study was a double-blinded (assessor and participants) controlled trial, the therapist was not blinded to group assignment, potentially introducing bias.

5. Conclusions

Applying 5 Hz rTMS to the affected hemisphere enhanced subsequent treadmill training effects on gait speed and spatial asymmetry. Improvements in gait speed persisted for at least 1 month in individuals with chronic stroke. These findings support the use of 5 Hz rTMS for effective treadmill training for gait improvement in people with chronic stroke.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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