Original Article

Immediate Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation Combined with Task-Specific Training in Individuals with Parkinson's Disease: a Preliminary Study

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ABSTRACT

Objectives: This study examined the immediate effects of a single-session of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) combined with task-specific training (TST) on reach-to-grasp (RTG) performance in individuals with Parkinson's disease (PD).
Study design: Matched-pair experimental design
Setting: Motor Control and Neural Plasticity Laboratory, Faculty of Physical Therapy, Mahidol University
Subjects: Twenty patients with mild to moderate severity of PD (Hoehn &Yahr stage I-III) participated in the study.
Methods: Participants were allocated into two groups. The experimental group received HF-rTMS to the left-primary motor cortex (M1) combined with TST of RTG, while the control group received only HF-rTMS to left-M1. Before and immediately post intervention, right-hand RTG performance was measured under no barrier and barrier conditions. Additionally, cortical silent period (CSP) was determined to verify the effects of HF-rTMS.
Results: There were no significant differences between the two groups for both RTG performance and CSP duration. In the control group, there was a significant decrease (p = 0.03) in movement time immediately after HF-rTMS for a barrier condition. Moreover, significant differences in absolute time to maximum aperture (TAmax) (p = 0.04) and temporal transport-grasp coordination (Tmax) (p = 0.04) were observed. A significantly longer CSP in the control group (p = 0.02) confirmed the effects of HF-rTMS. In contrast, the experimental group showed a significant prolonged in TAmax (p = 0.04) and Tmax (p = 0.05).
Conclusion: The findings in the experimental group indicated that the TST of RTG was not sufficient to augment the effects of HF-rTMS that may be the results of the complex task of RTG performance covering the aspect of RTG execution, planning, and transport-grasp coordination.

Keywords: transcranial magnetic stimulation, brain stimulation, bradykinesia, Parkinson's disease, task performance

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Introduction

Recently, the non-invasive brain stimulation technologies have been applied to be an alternative treatment for various neurologic and psychiatric conditions such as stroke, Parkinson's disease (PD) and depression.[1-3] In particular, repeti-tive transcranial magnetic stimulation (rTMS) has been increasingly used in both research and clinic. The rTMS is one of non-invasive brain stimulation technologies that can modulate corticospinal excitability and cortical inhibition in the cerebral cortex by the stimulation through the coil.[2]

Previous studies reported that the cortcospinal excitability and cortical inhibition could improve following a single-session of rTMS over the primary motor area (M1) not only in stroke condition[4] but also in individuals with PD.[2,5] Additionally, the upper extremity function especially reach-to-grasp (RTG) performance could be improved following a single-session rTMS over the M1.[2,4] However, long-term beneficial neuromodulation of rTMS is the limitation of a single-session of rTMS. The improvement of corticospinal excitability and motor performance has been observed following multiple sessions.[6] Alternatively, it has been identified that brain plasticity can be improved when HF-rTMS application precedes task specific-repetitive training (TST). Interestingly, the cortical excitability and the paretic hand performance in stroke were improved by a single-session of rTMS to M1 combined with TST as shown in previous studies.[7,8]

Based on the combined intervention model as applied in people with stroke, the TST was an indirect rehabilitation of the paretic limb following the rTMS primed the neural network that could be called "Bottom up approach".[6-8] This approach required a long period of treatment. The rTMS is considered a "top-down approach"[7] since it is directly applied

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to the central nervous system to reduce motor impairment.[4,5,7] In addition, compared to the former approaches, the rTMS may reduce the duration of treatment.[7] Therefore, if both approaches are combined, they most likely lead to a better motor performance as shown in the previous studies.[7,8] Previous evidence suggested that the specific type of motor training like a real world task led to neural plasticity and changed to the behavior.[7] Therefore, clinicians need to focus the specific motor impairment that is an important for becoming the specific type of motor training in each disorder.

Regarding individuals with PD, bradykinesia is one of the cardinal signs that is slowness of a performed movement.[9] The characteristics of bradykinesia are difficulty initiating and executing movement. Individuals with PD often complain of problems with performing manipulative tasks, in particular RTG performance deficits.[10] The RTG performance deficit is reflected by a longer movement time during RTG performance, a decrease in maximum velocity of the arm, an increase in time spent to decelerate the hand during grasping, a reduction of hand opening, and prolonged time between initiation of hand opening and maximal hand opening.[10] All of these impairments are reflected to the RTG execution and transport-grasp coordination. These impairments are magnified if the RTG task is performed under a barrier condition.[10] In term of RTG execution and transport-grasp coordination deficits, it might be a result of a basal ganglia-thalamocortical pathway deficit in nigrostriatal pathway that led to an increase in inhibitory signaling to the thalamus. Therefore, the thalamus cannot generate an excitatory signal to the M1 and supplementary motor cortices, which are the motor execution and planning areas, respectively.[2,11]

Regarding over inhibitory signaling to the motor cortex, it has been related with changes in cortical inhibition as represented by cortical silent period (CSP) duration. Compared to health people, the CSP duration was found to be shorter and intracortical facilitation reduced in people with PD.[12,13] Recently, it has been shown that high-frequency rTMS or HF-rTMS over M1 improved the CSP duration in individuals with PD. The rTMS application can be divided into two different frequencies including high-frequency and low-frequency. High-frequency rTMS should be referred to stimulus rates of more than 1 Hz. While low-frequency rTMS should be referred to stimulus rates of 1 Hz or less.[14] The HF-rTMS is used to increase corticospinal excitability and could restore the inhibitory system as indexed by the lengthening of CSP post HF-rTMS to M1.[2] In individuals with PD, there were several studies reported the HF-rTMS application could reduce the motor impairment.[2,15,16] In particular, the researchers demonstrated that the thalamocortical pathway deficit in nigrostriatal pathway could be compensated by the HF-rTMS application.[15] The HF-rTMS over M1 could reduce the motor impairment, representing by the improvement of motor part of unified Parkinson' disease rating scale (UPDRS),[5,17] movement time,[5,17] and reaction time.[17]

Additionally, following HF-rTMS to M1, many of the deficits for RTG execution when avoiding a barrier including total movement time (MT), deceleration time (DT), and transport maximum velocity (Vmax) improved. These variables reflect improvement in the transport component of RTG. Additionally, the grasping component was improved following HF-rTMS reflected by increased maximum aperture or hand opening (Amax) and time to maximum hand opening (TAmax).[2]

Taken together, the purpose of this preliminary study was to examine the immediate effects of a single-session of HF-rTMS over left-M1 combined with the TST using the RTG training (experimental group) on RTG performance in people with mild to moderate PD. We hypothesized that the experimental group would show greater improvement in RTG performance compared with the control group who received a single-session of HF-rTMS to left-M1 only. Moreover, we also investigated whether normalizing cortical inhibition is accompanied by improved RTG performance.

Methods

The study was approved by the Siriraj Institutional Review Board and the Mahidol University Institutional Review Board (MU-CIRB 2017/067.2003). This study was registered in the Thai Clinical Trials Registry (TCTR20170202002).

Participants

Individuals with PD were recruited from the Faculty of Medicine Siriraj Hospital and the Faculty of Physical Therapy, Mahidol University. Eligible participants had been diagnosed with idiopathic PD by movement disorders neurologists. All participants were right hand dominant (defined by Edinburgh Handedness Inventory) and were screened for inclusion and exclusion criteria. The inclusion criteria were as follows: (1) age range 40 to 80 years, (2) mild to moderate severity with Hoehn &Yahr (H&Y) stage I-III, (3) more impaired on the right hand dominant as examined by the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor examination) including items of rigidity, finger taps, hand movements, rapid alternating movements of the hands, tremor at rest, and action tremor of the hands, (4) ability to understand and follow simple commands with greater than 23 on the mini mental state examination (MMSE) Thai version 2002, and (5) ability to sit independently for more than one hour. The exclusion criteria were as follows: (1) contraindication for TMS confirmed by TMS screening questionnaire, (2) severe action or resting tremor with a score greater than or equal to 3 for action, postural, or resting tremor of the hands in the UPDRS part III, (3) severe rigidity with a score greater than or equal to 3 for rigidity of the hands in the UPDRS Part III, (4) ON/OFF medication fluctuations, (5) severe disability from dyskinesia with a score greater than or equal to 3 for dyskinesia in the UPDRS part IV, (6) other neurological and/or musculoskeletal problems affecting arm, hand, or trunk which would interfere with task achievement such as arthritis

in the upper extremity (UE), (7) implanted deep brain stimulation (DBS) or plan to have DBS during the study period, (8) psychiatric illness, alcohol or substance abuse, and (9) poorly controlled depression or anxiety (measured by the Thai Hospital Anxiety and Depression Scale (HADS) (score ≥ 11)). All participants were given a written informed consent and assessed before admittance into this study.

Study protocol

This study was a matched-pair experimental design. All participants were randomized into two groups, using a convenience sampling method (Figure 1). They were matched according to their impairment level and age range (+/-5 years). The experimental group received HF-rTMS over the left-M1 with RTG training while the control group received only HF-rTMS over the left-M1.

Moreover, both groups were assessed for RTG performance and cortical inhibition at baseline (Pre) and immediate post HF-rTMS with RTG training or post HF-rTMS only (Post) (Figure 1). Additionally, all participants were measured by the same evaluator. The evaluator was blinded (a single blinded clinical trial). During participation, they took their medications regularly. To control for medication in function, they were tested at the same time of day.

After evaluation at baseline, all participants in both groups received HF-rTMS over left-M1 at the extensor digitorum communis (EDC) representational area. The HF-rTMS application was produced from Magstim Rapid^2 (Magstim Co., Dyfed, UK) with the figure-of-8 air-cooled coil. The parameters for stimulation were shown in the previous study (Figure 1).[2] Importantly, HF-rTMS application was conducted by the same person to all participants.

After stimulation, the experimental group underwent TST of RTG which involved reaching to grasp a dowel of 1.2 centimeter in diameter. The RTG training was performed for 4 sessions consisting of 30 trials per session. They were allowed to take a rest for 5 minutes between sessions. During the training, the verbal instruction to focus on large amplitude movements was given every other trial to "reach the farthest and to open the hand the widest".

Outcome measures

The RTG performance of the right (more affected) hand was measured with an electromagnetic motion tracking system (Motion Monitor, Innsport, Inc, IL, USA). Three 3D sensors captured the kinematic data. The sampling rate for the three sensors was 100 Hz. A zero-lag Butterworth low-pass filter with a cut-off frequency of 20 Hz was used.[10] The researcher provided verbal instructions to the participants and demonstrated reaching and grasping the dowel with and without the barrier. Tasks were performed from less to more complex as determined previously. Thus, the order of task completion was without barrier condition to with the barrier. Regarding RTG measures protocol, it was shown in the previous study.[2]

All kinematic variables were extracted from each trial using customized automatic computer routines written in MatLab (the Math Works Inc., Natick, MA, USA). The RTG kinematic variables were used to determine the movement execution and visuospatial processing. Movement execution included total movement time (MT), deceleration time (DT), time to maximum aperture (TAmax), transport maximum velocity (Vmax) and maximum aperture or hand opening

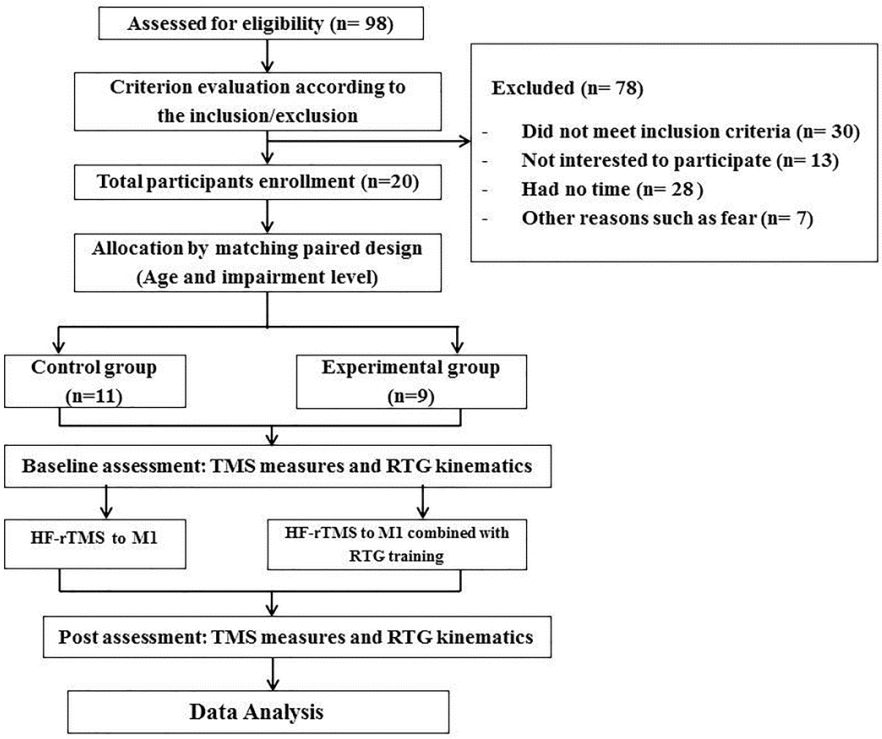

Figure 1. Diagram of the study protocol

(Amax). Visuospatial processing was measured by transport-grasp coordination that was expressed by the cross correlation coefficient (rmax) (spatial coordination) and the associated time lag (Tmax) (temporal coordination) between transport velocity and grasp aperture.[10]

The cortical inhibition was measured by the CSP duration; this is the duration of EMG interruption of voluntary motor activity and was generated using a single-pulse TMS with a figure-of-8 coil. Regarding CSP measures protocol, it was shown in the previous study.[2]

Statistical analysis

Mean and standard deviation was determined for the demographic data and clinical characteristics that were analyzed by descriptive statistics. The average of each variable was analyzed using independent sample t-test or Mann Whitney U-test. All data were analyzed by SPSS for window release 19.0 (IBM, SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk was used to determine normal distribution. As for the differences between the two groups, the independent t-test was used to analyze for the normal distributed data. In contrast, the Mann Whitney U-test was used to test for the non-normalization data. As for the data within each group, paired t-test was used to compare for cortical inhibition and RTG kinematics. In contrast, the Wilcoxon sign rank test was used to compare within each group for non-normally distributed data. The level of significance was set at a probability level equal to or less than 0.05 ($p \leq 0.05$). Effect size was used to quantify the magnitude of change following the stimulation. We calculated the effect size based on the statistical tools that were used in the study including Z score or t score and dividing it by the square root of the sample size per group. The effect size was classified as small (0.2), medium (0.5), and large (0.8).[18]

Results

Twenty individuals with PD who participated in this study were divided into two groups; control (n=11) and experimental (n=9) groups. The characteristics and demographic data are shown in the Table 1. All of the participants were more affected on the right side and their age was between 50-80 years old. In addition, based on UE impairment, participants were identified as H&Y stages I, II, and III with 1, 15, and 4 individuals/stage, respectively. Scores for right UE impairment from the UPDRS-Motor section ranged from 3-18 (total UE score = 24). Additionally, there were no significant differences in age, disease duration, UPDRS UE score, MMSE, HADS scores, and medications ($p > 0.05$) between the two groups (Table 1).

Mean (standard error, SE) of all baseline and post intervention kinematic measures between the two groups for the non-barrier and the barrier conditions are shown in Figure 2 and 3. At baseline, there were no significant differences in any kinematic variables between the two groups. These baseline findings indicates homogeneous participants. The differences in RTG execution are presented in Figure 2 and 3.

No group differences were found in the movement time (MT) and absolute deceleration time (DT) for both conditions. However, the control group demonstrated a significant decrease in MT for the barrier condition ($p = 0.03$) with a medium effect size (ES = 0.53) (Figure 2B). While no significant differences were observed in the experimental group for the non-barrier and barrier conditions (Figure 2A-2B). Additionally, the control group showed a significant decrease in the absolute DT for the barrier condition ($p = 0.03$) with a medium ffect size (ES = 0.56) (Figure 2D), but not found in the experimental group (Figure 2D).

For Transport maximum velocity (Vmax), there were no significant differences between the two groups and within each group for both conditions. However, the control group showed a non-significant increase in Vmax following M1 stimulation only compared to the baseline for both conditions. While, there was no change in the experimental group (Figure 2E-2F).

While no group differences were found in the hand opening or maximum aperture (Amax) and transport to maximum aperture (TAmax) for both conditions. The Amax in the control group showed a near significant increase following

Table 1. Comparison of the characteristics and demographic data

	Control group (n=11) Mean (SD)	Experimental group (n=9) Mean (SD)	*p*-value
Age (years)	66.91 (7.49)	64.44 (8.26)	0.49[a]
Disease duration (years)	9.27 (6.21)	7.44 (4.85)	0.48[a]
UPDRS (III-right UE UE, scores)	12.55 (4.01)	12.89 (2.98)	0.83[a]
Thai-MMSE (scores)	25.73 (1.27)	25.44 (1.42)	0.65[a]
HADS-Anxiety (scores)	3.09 (2.07)	3.11 (2.37)	0.98[a]
HADS-Depression (scores)	4.18 (1.99)	2.56 (1.94)	0.08[a]
Medications			
Levodopa, mg/day	659.09 (267.17)	541.67 (165.36)	0.27[a]
COMT inhibitor, mg/day	475 (95.74)	475 (95.74)	0.73[b]

[a]*p*-value from Independent sample t-test, [b]*p*-value from Mann Whitney test, *significant difference at *p*-value ≤ 0.05
COMT; catechol-O-methyltransferase inhibitor

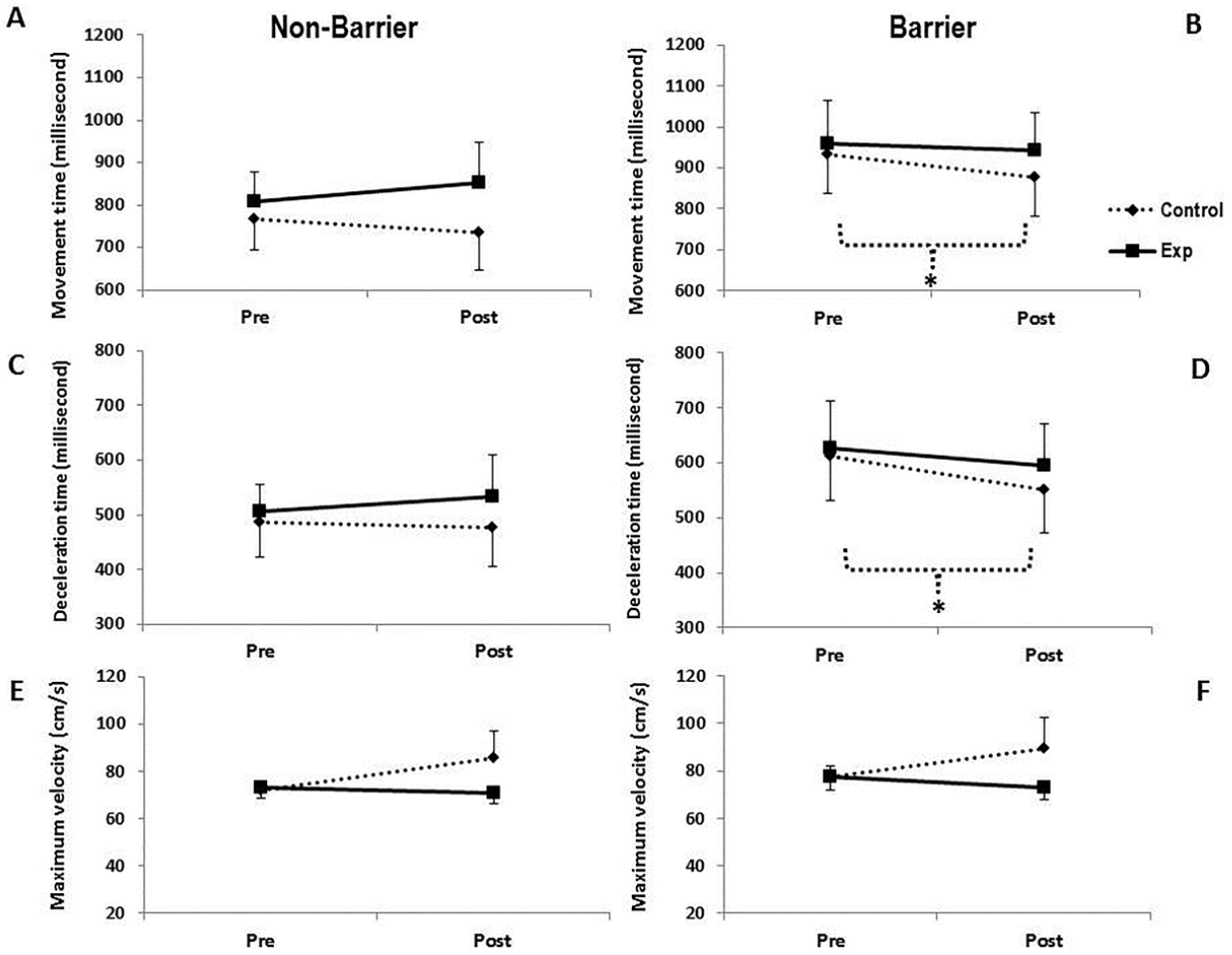

Figure 2. Average (+/-SE) movement time (A and B), absolute deceleration time (C and D), and maximum velocity (E and F) at baseline (pre) and immediately post intervention (post) for the experimental and control groups in non-barrier (left) and barrier (right) conditions

HF-rTMS compared to baseline in the barrier condition (p = 0.06) with a medium effect size (ES = 0.40). In addition, no change was observed in the experimental group. (Non-barrier condition: experimental group pre = 5.23 (0.34) cm/ post = 5.17 (0.54) cm and control group pre = 5.85 (0.52) cm/ post = 5.73 (0.65) cm/Barrier condition: experimental group pre = 4.59 (0.36) cm/post = 4.64 (0.5) cm and control group pre = 4.74 (0.48) cm/post = 5.28 (0.62) cm). Additionally, the control group demonstrated a significant decrease in absolute TAmax in the barrier condition (p = 0.04) with a medium effect size (ES = 0.49) (Figure 3B). In contrast, the experimental group showed a significant longer in TAmax following combined interventions compared to the baseline in the non-barrier condition (p = 0.04) with a large effect size (ES = 0.81) (Figure 3A).

Regarding the temporal coordination or Tmax, there were no group differences for both conditions. However, the control group showed a significant decrease in Tmax compared to the baseline for the barrier condition (p = 0.04) with a medium effect size (ES = 0.50) (Figure 3D). In contrast, the experimental group showed a prolong significant in Tmax compared to the baseline for the non-barrier condition (p = 0.05) with a medium effect size (ES = 0.54) (Figure 3C).

For spatial coordination, there were no significant differences between the two groups and within each group for both conditions. (Non-barrier condition: experimental group pre = 171.77 (23.44) ms/post = 198.45 (31.61) ms and control group pre = 161.7 (23.53) ms/post = 172.65 (22.33) ms /Barrier condition: experimental group pre = 272.71 (37.01) ms/post = 253.95 (34.21) ms and control group pre = 247.07 (29.36) ms / post = 215.32 (26.47) ms).

Regarding the cortical inhibition (TMS measure), it was represented by the CSP duration. There was no significant difference between the two groups. However, there was significant difference between pre and post measurement following the HF-rTMS to M1 (p = 0.02) for the control group, but not in the experimental group who received the HF-rTMS to M1 combined with the RTG training (p 0.11) (Figure 4).

Discussion

This study examined the immediate effects of a single-session HF-rTMS over M1 with task specific-repetitive RTG training (experimental group) on RTG performance in people with PD with mild to moderate upper extremity impairment. Their RTG performance was compared to the control group who was stimulated by HF-rTMS to M1. The findings in the

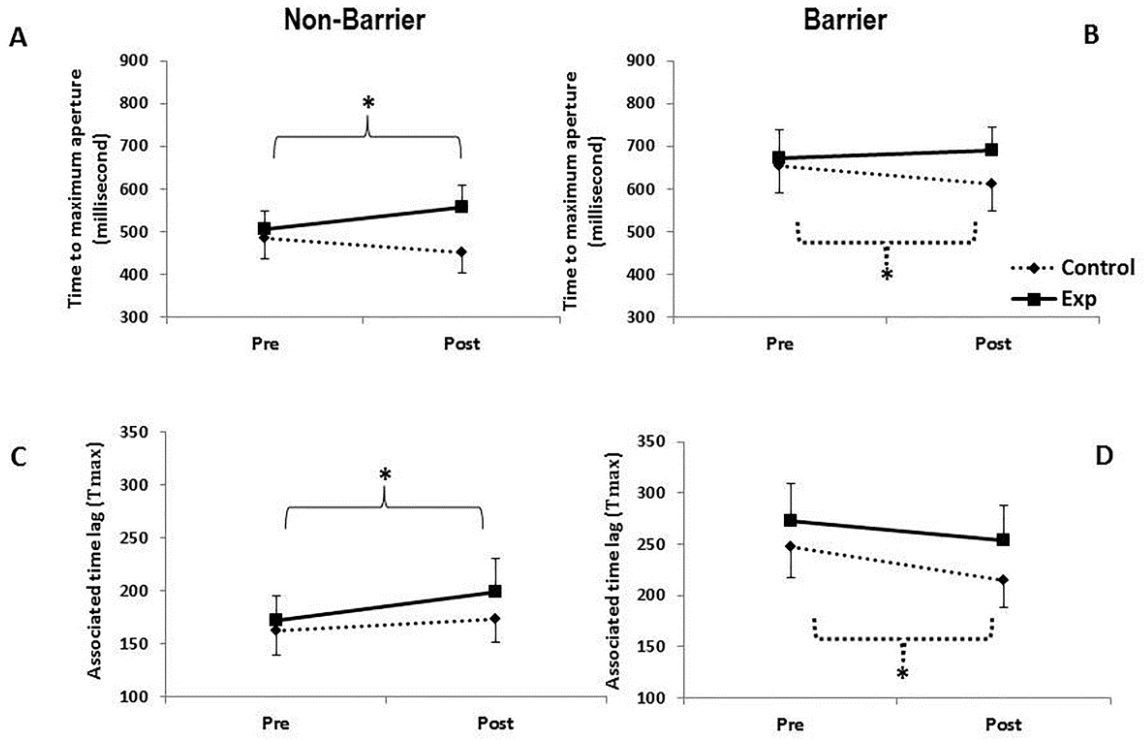

Figure 3. Average (+/-SE) time to maximum aperture (A and B) and associated time lag (C and D) at baseline (pre) and immediately post intervention (post) for the experimental and control groups in non-barrier (left) and barrier (right) conditions

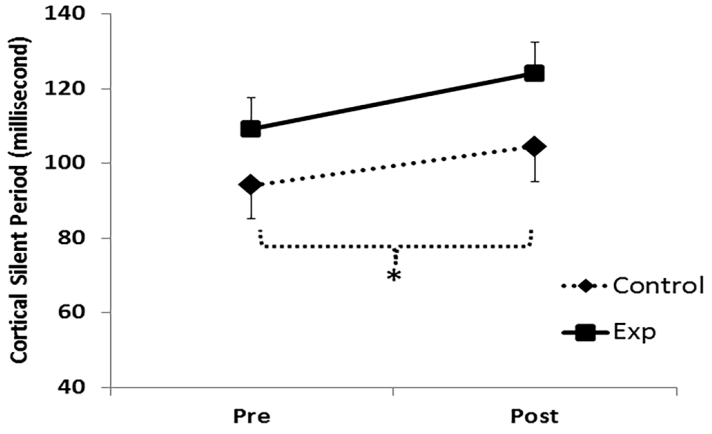

Figure 4. The average (+/-SE) cortical silent period at baseline (pre) and immediately post intervention (post)

control group are consistent with our hypothesis of improvement in RTG performance following HF-rTMS to M1. The HF-rTMS over M1 improved RTG execution with respect to speed as evidenced by decreased MT, DT, and TAmax. Additionally, temporal transport-grasp coordination or Tmax nearly improved following HF-rTMS to M1. In particular, there were significant differences in the barrier condition. These data suggest that HF-rTMS over M1 can directly improve RTG performance, particularly for the most challenging task. Regarding the significant improvement of RTG performance following HF-rTMS to M1, it may be the result of restoration of the inhibitory system by activating dopamine (DA) release through M1 stimulation. From a physiology of HF-rTMS with the parameters used over M1, the previous evidence demonstrated DA release in the striatum was observed following a single-session of stimulation.[2,19,20] The DA release would send back to the nigrostriatal pathway and restored the function between thalamus and motor cortex as evidenced in the previous study.[2] This possible mechanism was verified by an increase in the cortical inhibition as indexed by a significant lengthening of CSP duration seen immediately post HF-rTMS to M1. The finding in the control group was consistent with a previous study.[2]

In the experimental group, the main findings regarding RTG performance is not consistent with our hypothesis because there were no significant improvements following HF-rTMS to M1 combined with RTG training. In addition, a decrease in processing speed based on the prolonged

TAmax, and Tmax observed immediately post combined intervention compared to baseline. Five possible explanations were as follows: (1) type of verbal instruction, (2) a single combined session, (3) the number of trials for improving the different neural control of reaching only versus RTG performance, (4) level of task difficulty for training, and (5) the location of stimulation. The detail of each notion is described in the following paragraphs.

First, the unexpected results may be a result of the verbal instruction. In this study, the amplitude-focused instruction was given during RTG training that was not specific for improving movement speed.[21] Additionally, the verbal instruction might increase the working memory load that can lead to a deterioration of motor performance immediately post training.[22] Secondly, a single combined session might not be sufficient to improve performance. Based on a previous study, individuals with PD improved gait immediately following 12 combined sessions.[23] Thirdly, the number of trials in this study was not sufficient to enhance motor learning during a complex task such as RTG. The 120 trials used in this study is based on a study that successfully utilized rapid arm reaching only training.[24] The neural control of reaching and grasping an object is more complex and requires more coordination.[25,26] The RTG movement requires precise control in two components including transport component for moving forearm and hand to a specified object and grasp components for shaping the hand to grasp the object. Additionally, these components need to be coordinate temporally and spatially.[10] In previous evidence, individuals with PD usually had RTG deficits in term of motor planning, motor execution and transport-grasp coordination.[10]

Fourthly, the RTG training in this study may be less difficult than improving the motor planning and transport-grasp coordination. Insights into the pathophysiology perspective in individuals with PD, motor execution deficit may be a result of DA deficit in nigrostriatal pathway. As for the motor planning and transport-grasp coordination, it may be a result of DA loss in the ventral tegmentum area (VTA) of the mesocortical pathway. This impacted on the transmission of DA to the prefrontal cortex,[11] in particular dorsal lateral prefrontal cortex (DLPFC).[27,28] The prefrontal area is responsible for higher order planning, decision making, movement selection, and attentional processing.[29] In particular, in its role in executive function, DLPFC is associated with working memory[30] and cognitive flexibility.[31] Therefore, a DA deficit along the mesocortical pathway leads to inability to plan, initiate, and monitor goal-directed behavior with the flexibility to update goals when presented with new information.[32] Regarding the RTG training in this study, it was not specified to reduce the motor impairment in term of motor planning and RTG transport-grasp coordination. Individuals with PD need to improve their executive function through the prefrontal cortex function. In addition, the RTG training in this study may be less difficult than the RTG performance testing as measured in the barrier condition. Therefore, it may not support the prefrontal cortex function in term of the flexibility to update goals when presented with new information.[32]

Finally, in addition to the RTG training, the location for stimulation in the experimental group may not support TST in term of motor planning and RTG transport-grasp coordination as measuring by the temporal transport-grasp coordination. The HF-rTMS to M1 could improve only motor execution as shown in a recent study.[2] Therefore, M1 stimulation was not sufficient to improve the executive function as impaired by a DA loss in mesocortical pathway. Therefore, DLPFC stimu-lation may be suggested in the further study for improving the motor planning and RTG transport-grasp coordination. Additionally, the DA deficit in individuals with PD, this impacted on the interconnected brain regions that include reduced activity in the supplementary motor cortex and reduced efferent feedback in the basal ganglia-thalamocortical pathway. Accordingly, in addition to the DLPFC stimulation, additional stimulation over the supplementary motor cortex may be suggested in further study to improve motor planning and RTG transport-grasp coordination through the connection between the supplementary motor cortex and the basal ganglia function that plays a role in the kinematic scaling of movements.[15,33]

Additionally, the non-improvement of RTG performance in the experimental group has also been shown to be accompanied by the non-significant lengthening of CSP duration compared to the baseline. The authors expected the combination of HF-rTMS and TST would increase the cortical inhibition, but our resulted did not showed a significant difference. Even though, a single-session of HF-rTMS over left-M1 could induce a significant lengthening of CSP duration. A single combined session could not improve the inhi-bitory system. The possible explanation may be a result of a single-session of TST of RTG. Because of the TST, the previous study found that the inhibitory system can be enhanced following the 2-weeks TST of balance training on an unstable platform when compared to a control group performing a normal routine of physical activity.[34]

There were some limitations in our study. Firstly, regarding the unexpected results in the experimental group, the 120 trials used for training in this study was not sufficient to improve motor learning during RTG actions, due to their complexity and requirement for coordination.[26] Thus, the improvement of RTG actions may require more trials. Secondly, regarding the prolonged TAmax and temporal transport-grasp coordination, it may be the result of internal programming deficits. According to the DA deficit in the mesocortical pathway leading to inability to plan motor performance, the DLPFC stimulation may suggest for the future study to improve DA release in that pathway. Alternatively, the RTG training specifically induced executive function may be suggested for the future study. Thirdly, a single-session of HF-rTMS in conjunction with TST was not sufficient to

improve motor performance, so several sessions are suggested for future studies. Beneficial effects of the combined intervention is the long-term effects.[8] Previously, the paretic hand in individuals with stroke improved and their improvement persisted at least 2 weeks following a single-session rTMS with TST.[8] Therefore, a long-term effect is suggested to measure for a further study. Finally, according to a preliminary study, the sample size was small and participants were not homogeneous. Therefore, results to support the combined intervention or the HF-rTMS only could be definitively determined with a large sample size and more homogenous group.

In conclusion, the preliminary findings demonstrated that a single session of HF-rTMS on M1 combined with TST was not sufficient to improve the complex task of RTG performance in individuals with mild to moderate PD. It may be the result of the RTG training in this study because it may not sufficient to improve the aspect of RTG planning and transport-grasp coordination as they showed a prolonged TAmax and Tmax. Even though, the RTG execution could be improved following a single session of HF-rTMS to M1.

Disclosure

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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