Reach-to-Grasp Training in Individuals with Chronic Stroke Augmented by Low-Frequency Repetitive Transcranial Magnetic Stimulation

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Objective: *The present study investigated the immediate effects of low frequency repetitive transcranial magnetic stimulation (LF-rTMS) combined with reach-to-grasp (RTG) training of the paretic hand in individuals with chronic stroke.*
Material and Method: *Fourteen participants were randomly assigned to receive LF-rTMS or sham stimulation conditions. All participants underwent RTG training after the stimulation. Corticospinal excitability (CE) of the non-lesioned hemisphere, the total time of the wolf motor function test (WMFT) for dexterity tasks, maximum aperture, and movement time of RTG actions were evaluated at baseline, after the stimulation, and after RTG training.*
Results: *Significant differences between interaction (group x time) were found in the total time of WMFT. The CE of non-lesioned hemisphere diminished after LF-rTMS and showed moderate correlation with the reduction in time of RTG actions after the stimulation. The total time of WMFT and RTG actions reduced after motor training only in the LF-rTMS group. No change was observed in maximum aperture in either group.*
Conclusion: *The application of LF-rTMS combined with RTG training enhanced the training effect as evidenced by faster movement for the dexterity tasks of the paretic hand than RTG training alone. The findings suggested the benefit of LF-rTMS for enhancing the training effects in stroke rehabilitation.*

Keywords: *Non-invasive brain stimulation, Motor training, Stroke*

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Stroke is the third leading cause of death in Thailand[1]. Approximately 60% of individuals with stroke suffer from arm disability[2], leading to inability to perform activities of daily living. Studies have reported that low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) could improve hand functions of individuals with stroke[3-5]. The investigations have studied the effect of LF-rTMS for reducing over-excitability of inter-hemispheric inhibition from the non-lesioned hemisphere to the lesioned hemisphere. LF-rTMS reduced neural excitation of the non-lesioned hemisphere and improved paretic hand functions. Takeuchi and co-workers combined LF-rTMS and pinch training in individuals with chronic stroke and reported that the LF-rTMS induced increased excitability of the lesioned motor cortex and improved the pinch acceleration of the paretic hand. The effect of pinch training was enhanced by LF-rTMS[6]. The additive effect of LF-rTMS and motor training requires investigation in real-world tasks. Whether augmenting motor training of a more complex skill like reach-to-grasp (RTG) actions with LF-rTMS would improve hand function remains unknown. The aim of the present study was to investigate the effect of LF-rTMS on RTG training in individuals with chronic stroke.

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Material and Method

Subjects with chronic stroke were recruited in the present study. The inclusion criteria included 1) single stroke with stroke onset more than six month, 2) right hand dominance, 3) able to perform reach-to-grasp action with their paretic arm, and 4) moderate arm impairment. Subjects not meeting the safety criteria for using rTMS were excluded.

Participants were randomly divided in the experimental group (active LF-rTMS plus RTG training) or the control group (sham LF-rTMS plus RTG training). All participants understood and signed informed consent forms approved by the Mahidol University Institutional Review Board (MU-IRB 2012/070.1004).

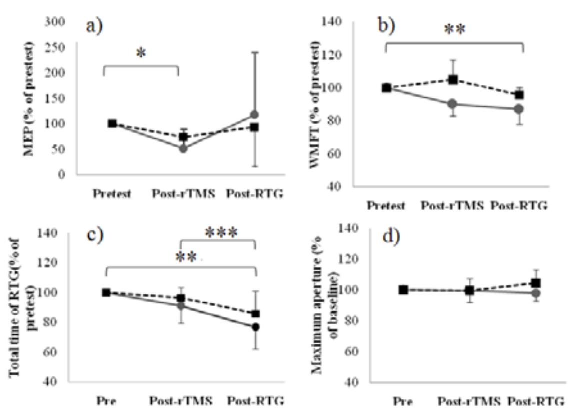
Corticospinal excitability (CE), total time of the wolf motor function test (WMFT), maximum aperture and total time of RTG actions were assessed at pretest, after LF-rTMS stimulation and after RTG training. The CE was measured by peak-to-peak amplitude of motor evoked potential (MEP) at an intensity equal to 120% of the resting motor threshold (rMT). The location of LF-rTMS stimulation was a hot spot of the abductor pollicis brevis muscle at M1 of the non-lesioned hemisphere. Surface electromyography (Medelec Synergy, VIASYS Health Care Inc., Surrey, UK) was used to record the MEP. A digital camera and stopwatch were used to measure the movement time of WMFT for dexterity tasks (consisting of lifting a can, lifting a pencil, lift a paper clip, stacking checkers, turning a key in a lock and folding a towel), and the maximum aperture and total time of RTG actions.

For the experimental active LF-rTMS group, rTMS was applied by a figure of eight air-cooled coil attached with Magstim rapid[2] (Magstim Co., Dyfed, UK) and the frequency was set at 1Hz, intensity 90% of rMT for 20 minutes (1,200 pulses). For the control sham rTMS group, the same rTMS coil was set at the same location as the LF-rTMS group, but the coil was tilted 90 degrees to the scalp (sham manipulation[7]) using the same intensity and frequency as active LF-rTMS. The sham group heard clicking sounds from the rTMS coil during the 20 minute-duration but received no stimulation.

For the RTG training, participants were asked to grasp and release a can placed 15 cm anteriorly from their hand. The frequency was controlled at 12 times per minute by a metronome. Each time of grasping, the participants were informed to grasp gently the can. A blood pressure cuff was used as feedback, and the grasping force was controlled at 10 mmHg. The training protocol was as follows: training for 5 minutes and resting for 2 minutes per 1 session, totaling 6 sessions. The Kolmogorov-Smirnov goodness-of-fit test was used to test the distribution of the data. The data were normally distributed. Two-way mixed ANOVA was used to compare MEP, total time of WMFT, maximum aperture, and total time of RTG actions. Bonferroni correction was used for a post hoc multiple comparison analysis. Pearson's correlation coefficient was used to determine the relationships between changes in the CE and changes in behavioral outcomes.

Results

The numbers of subjects in each group were seven. The subjects were between 49 and 69 years (57.8±5.5), with time poststroke 6-109 months (43±42), and Fugl-Meyer assessment (arm section) scores between 39 and 50 points (45.14±3.7). No participant reported any adverse effects throughout the study. Significant main effects were found regarding time, group and interaction (group x time) on the total time of WMFT ($p = 0.004$, $p = 0.008$, $p = 0.014$, respectively). Additionally, a main effect was observed in the group regarding the total time of RTG actions ($p<0.001$). The post hoc analysis showed significant reduction in the following variables: 1) the MEP of the non-lesioned hemisphere in the experimental group at post test after active LF-rTMS stimulation (post-rTMS) compared with pretest ($p = 0.004$, Fig. 1a), 2) the total time of WMFT in the experimental group at post test after motor training



* = significant difference ($p<0.05$) between pretest and post-rTMS in rTMS group
** = significant difference ($p<0.05$) between pretest and post-RTG in rTMS group
*** = significant difference ($p<0.05$) between post-rTMS and post-RTG in rTMS group

Fig. 1 Corticospinal excitability and motor behavior change (percent of pretest) at pretest, Post-rTMS, Post-RTG, (a) MEP, (b) WMFT, (c) Total time of reach-to-grasp, (d) Maximum aperture,* = significant difference p<0.05, --■-- = Control group, —●— = rTMS group.

(post-RTG) compared with pretest ($p = 0.001$, Fig. 1b), 3) the time of RTG actions in the experimental group post-RTG compared with post rTMS, and post-RTG compared with pre-test ($p = 0.049$, $p = 0.004$, Fig. 1c). No change was observed in maximum aperture (Fig. 1d). In addition, a moderate correlation was found between reduction in MEP amplitude of the non-lesioned hemisphere and reduction in total time of RTG actions (r = 0.645, $p = 0.118$). In contrast to the findings of the experimental group, no significant changes were found in the control group.

Discussion

The authors demonstrated that motor training in individuals with stroke was enhanced by the application of LF-rTMS to decrease the CE of the non-lesion hemisphere. We extended the work of Takeuchi et al[6] by combining LF-rTMS and 42 minutes of real world task like RTG training. The combined effects of LF-rTMS and RTG training resulted in the reduction of movement time of RTG actions and the total time of dexterity in the WMFT. These findings were not observed in the control group.

The result of the present study was similar to the recent study of Tretriluxana et al[5] that decreasing CE in the non-lesioned hemisphere from LF-rTMS (down-regulated effect of LF-rTMS) resulted in faster RTG actions. The authors did not observe an increase in maximum grasp aperture. One possible explanation could come from the difference in target muscle stimulation. They targeted the extensor digitorum communis muscle, an agonistic muscle for wrist extensors and finger hand opening while we targeted abductor pollicis brevis muscle, a prime mover of thumb abduction.

The LF-rTMS was effective to reduce CE of the non-lesioned hemisphere as evidenced by a decrease in amplitude of MEP after rTMS, which was not found in the sham, stimulation, condition group. Similar to previous studies[3-5], decrease in CE of the non-lesioned hemisphere contributed to improvement in function of the paretic hand. The down-regulated effect of LF-rTMS increased the effect of motor training and might rebalance interhemispheric inhibition[3-6,8]. The use of LF-rTMS before motor training might prime the environment of the neural activity in the lesioned hemisphere making it more suitable for plasticity adaptation than motor training alone[6]. The other possible mechanism might be the combined effect of LF-rTMS and RTG training in the present study could accumulate increased neural activity in the lesioned hemisphere. The motor training induced the increase of cortical excitability of the lesioned hemisphere[9], while the effect of LF-rTMS eliminated the inter-hemispheric inhibition from the non-lesioned hemisphere leading to greater cortical excitability of lesioned hemisphere[10]. The enhancement of neural activity of motor cortex influences motor relearning[11].

The authors investigated the immediate effect of LF-rTMS combined with RTG training. Therefore, a longitudinal study or the application of LF-rTMS and other functional trainings such as fine movement of hand or a study with a large number of subjects might be conducted.

In conclusion, the authors have shown the benefit of the combined effect of LF-rTMS and RTG training to promote the recovery of the paretic hand after stroke. The application of LF-rTMS is suggested for maximizing the effect of motor training in stroke rehabilitation.

What is already known in this topic?

The over excitability of inter-hemispheric inhibition from non-lesioned hemisphere onto lesioned hemisphere interferes the motor learning after stroke. The previous study reported that the LF-rTMS rebalanced the inter-hemispheric inhibition and improved the simple hand functions such as pinching movement.

What the study adds?

The study extended previous studies by combining the LF-rTMS with real world task like reach-to-grasp training. The application of LF-rTMS reduced reach-to-grasp and hand functional movement time. The results of this study indicate the benefit of applying LF-rTMS in conjunction with hand functional training in stroke rehabilitation.

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Potential conflicts of interest

None.

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การกระตุ้นสมองผ่านกะโหลกศีรษะด้วยคลื่นแม่เหล็กไฟฟ้าความถี่ต่ำแบบซ้ำเพื่อเสริมผลการฝึกเอื้อมหยิบของในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง

ปริญญา ว่องไววณิชกุล, นราวุฒิ ภาคาพรต, จารุกุล ตรีไตรลักษณะ, สุนีย์ บวรสุนทรชัย, วิภาวี ลักษณากร

วัตถุประสงค์: *ศึกษาผลทันทีของการกระตุ้นสมองด้วย LF-rTMS ร่วมกับการฝึกเอื้อมหยิบของด้วยมือข้างอ่อนแรงในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง*

วัสดุและวิธีการ: *สุ่มผู้ร่วมศึกษาจำนวน 14 ราย เข้ารับการกระตุ้นสมองด้วย LF-rTMS หรือการกระตุ้นหลอก ภายหลังการกระตุ้นทุกคนได้รับการฝึกเอื้อมหยิบของ ทำการประเมินระดับความสามารถของสมองต่อการถูกกระตุ้น (CE), เวลาในการทำกิจกรรม wolf motor function test (WMFT) หมวดงานละเอียดอ่อน, ความกว้างมากที่สุดของการกางนิ้วมือ และที่ก่อนและหลังการกระตุ้น และหลังการฝึกเอื้อมหยิบทันที*

ผลการศึกษา: *พบความต่างอย่างมีนัยสำคัญทางสถิติของความสัมพันธ์ระหว่างเวลาที่ใช้ในการทำกิจกรรม WMFT นอกจากนี้เวลาของตัวแปรเวลาการเอื้อมหยิบและเวลาที่ใช้ในการทำกิจกรรม WMFT ลดลงหลังการฝึกเอื้อมหยิบในกลุ่มที่ได้รับ LF-rTMS เท่านั้น หลังการกระตุ้นระดับของ CE สมองข้างไม่มีรอยโรคลดลงทันทีและมีความสัมพันธ์ระดับปานกลางกับการลดลงของเวลาเอื้อมหยิบ แต่ไม่พบการเปลี่ยนแปลงความกว้างการกางนิ้วมากที่สุดทั้งสองกลุ่ม*

สรุป: *LF-rTMS ร่วมกับการฝึกเอื้อมหยิบเพิ่มผลของการฝึกโดยทำให้มือข้างอ่อนแรงทำงานได้เร็วกว่า การฝึกเพียงอย่างเดียว ดังนั้นจึงบ่งชี้ผลดีของการนำ LF-rTMS ประยุกต์ใช้เพื่อเพิ่มผลการฟื้นฟูผู้ป่วยโรคหลอดเลือดสมอง*