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Effects of Hand Individual Finger Exercise after 1 Hz Low-Frequency rTMS on Cerebral Motor Evoked Potential and Latency in Patients with Stroke

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This study aimed to investigate the effects of individual finger exercise under the residual effect after low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) on cerebral motor-evoked potential amplitude (MEP amplitude) and cerebral MEP latency (MEP latency) in patients with stroke. This study conducted an intervention program in two groups of patients with chronic stroke (experimental group, individual finger exercise including residual effect after LF-rTMS group; IFE-rTMS group, individual finger exercise; IFE group, each comprising 10 patients). The program, which was conducted five times a week for 1 week, evaluated the MEP amplitude and MEP latency before and after the experiment. In an inter-group test of MEP amplitude and latency, all groups demonstrated an increase between the pre- and post-test evaluations. In an inter-group examination of MEP amplitude and latency, a significant difference was observed between the IFE-rTMS and IFE groups.

Keywords : low frequency repetitive transcranial magnetic stimulation (LF-rTMS), motor-evoked potential amplitude (MEP amplitude), motor-evoked potential latency (MEP latency), stroke, finger exercise

1. Introduction

Stroke is the most common neurological disease and is defined as a local or general acute clinical abnormality caused by cerebral ischemia or hemorrhage [1]. After a stroke, active movement is possible within 3-6 months, and motor function tends to recover from the proximal to the distal part of the body [2]. Serious damage caused by stroke includes limitation and loss of motor control. Weakness of the distal muscles affects motor dysfunction [3]. Increased muscle tension and decreased motor control ability in the injured upper extremity after a stroke cause delays in the initiation and termination of contraction of the flexor and extensor muscles and problems with movement coordination. This interferes with normal limb movements and negatively affects the skills necessary for daily living. Hence, it acts as a factor that hinders recovery of motor function of the upper limbs, including the fingers, and return to daily life [4].

Functional imbalance within the motor system following stroke [5] can be caused by damage to the white axonal tracts connecting the brain motor areas [6]. In particular, after onset, many patients develop upper limb and hand movement disorders on the contralateral side of the damaged cerebral hemisphere owing to damage to the corticospinal tract [7]. The corticospinal tract mainly controls the distal muscles in the body to control distal movements such as finger and toe movements, and damage to the corticospinal tract affects the dexterity of the distal part of the body [8]. Recently, several rehabilitation methods have been introduced to improve hand function in patients with stroke. Among these, repetitive transcranial magnetic stimulation (rTMS) has been introduced as an upper-extremity treatment method for patients with hemiplegia after stroke [9, 10]. Transcranial magnetic stimulation (TMS) uses the principle of placing an electromagnetic coil on the outer skin of the head, shortly generating a magnetic field, changing it into an electric field within the tissue, and causing depolarization of nerve cells located in the cerebral cortex when the electric field wave reaches the appropriate intensity and time [11, 12]. Additionally, rTMS is used to evaluate the residual function of the corticospinal tract after stroke [13]. Motor-evoked potential (MEP) testing using TMS can directly evaluate the function of the motor nerve pathway by stimulating pyramidal neurons in the cerebral

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cortex [14].

Recent studies have reported that treatment methods that apply various treatments together with rTMS effectively improve upper extremity function in patients with stroke. Shim and Lee have reported that when high-frequency rTMS (10 min) on the injured side and motor learning (10 min) related to upper limb and hand movements were applied together in patients with subacute stroke three times a week for 4 weeks, finger grip strength decreased. Moreover, a significant improvement was observed compared to that in the control group [15]. In particular, the intrinsic muscles in the hand provide stability for finger movements [16]; although the size and number of muscles in the hand are small, they generate a powerful force equivalent to approximately 50 % of the entire grip strength of the hand [17]. In addition, Zijdewind and Kemell have reported that finger exercises in patients with stroke effectively improved upper extremity and hand function [18]. In addition, according to Ma's study in 2017, when task-oriented activities were provided to stroke patients, the MEP of hand muscles improved, and scores also improved in the Manual Function Test (MFT) and Box and Block Test (BBT), which are functional tests of the hand [19]. reported. According to a study by Thut and Pascual-Leone, when low-frequency rTMS (LF-rTMS) was performed with an average stimulation intensity of 101 % MT (80 %-110 % motor threshold), the average stimulation duration was 31 min [20]. Therefore, based on these previous research results, we performed individual finger movements within the residual effect duration after LF-rTMS (1 Hz) on the motor cortex of patients with stroke on the damaged side. Changes were analyzed by measuring the MEP amplitude and MEP latency, and these neurological changes were used to provide another rehabilitation treatment method for patients with stroke.

2. Theoretical Background

2.1. Principles and effects of LF-rTMS

TMS shortly generates a magnetic field after placing an electromagnetic coil on the outer skin of the head, which changes into an electric field within the tissue. When the electric field reaches the appropriate intensity and time, it depolarizes the nerve cells located in the cerebral cortex. This method uses the principle of causing [21]. The intensity of TMS magnetic stimulation is not weakened by high-resistance objects such as the skull or scalp and does not form a strong current density in the scalp, resulting in less pain, making it possible to safely and effectively control the cerebrum non-invasively [22].

rTMS, which involves repeated TMS stimulation, has longer-lasting effects than the initial stimulation period. rTMS can increase or decrease the excitability of the corticospinal tract, depending on the intensity of stimulation, coil direction, and frequency. Although the mechanism underlying this effect is unclear, it may cause changes in synaptic efficacy, similar to long-term potentiation and long-term depression. rTMS stimulates at a high frequency of 5-20 Hz, depending on the stimulation frequency, and increases the response of the cerebral cortex, as confirmed by a decrease in the MEP threshold. Low frequency is defined as ≤ 1 Hz. Alternatively, stimulation at the same frequency can inhibit the cerebral cortical response [23-25].

A previous study has reported that LF-rTMS inhibits the activation of the cerebral cortex on the non-damaged side by stimulating the cerebral cortex on the non-damaged side, thereby enhancing the activation of the damaged side of the brain, which can have a positive effect on the recovery of upper limb function and motor learning [26].

A study on the duration of the effect of TMS has reported that when LF-rTMS was performed with an average stimulation intensity of 101 % MT (80 %-110 % motor threshold), the average stimulation duration was 31 min [20].

3. Methods

3.1. Subjects

The research period of this study was from February to May 2023, and the participants were adult patients with stroke hospitalized at the Department of Rehabilitation Medicine at O Hospital in Gyeonggi-do who received rehabilitation treatment. Altogether, 24 patients were selected, of which four were excluded because they did not meet the inclusion criteria, resulting in a total of 20 participants. The selected patients were randomly grouped into two by drawing lots, with each group comprising 10 people. The study selection criteria were as follows: diagnosed with stroke (cerebral hemorrhage and cerebral infarction) through computed tomography or magnetic resonance imaging; died > 6 months since stroke onset; and voluntary participation after providing informed consent.

The following exclusion criteria were in line with Rossi et al.'s recommendations to prevent side effects when using rTMS [27]: with a pacemaker, intracardiac wire, or metal implant; with a metal object on the head; with clinically unstable medical disorders, such as seizures; with internal carotid artery damage; and with aphasia or

cognitive impairment that can make evaluation difficult, hemineglect and visual field defects, or psychiatric or orthopedic diseases.

3.2. Intervention method

After examining the general information of the 20 patients who met the selection criteria for this study, 10 patients were assigned to each group by drawing lots. The selected patients were divided into the experimental group, the individual finger exercise group after LF-rTMS (hereinafter referred to as IFE-rTMS group, experimental group), and the control group, the individual finger exercise group (hereinafter IFE group, control group).

The IFE-rTMS group received intervention for a total of 30 min, consisting of 20 min of LF-rTMS at 1 Hz and 10 min of individual finger exercises. Meanwhile, the control and IFE groups only performed individual finger exercises for a total of 30 min (Table 1).

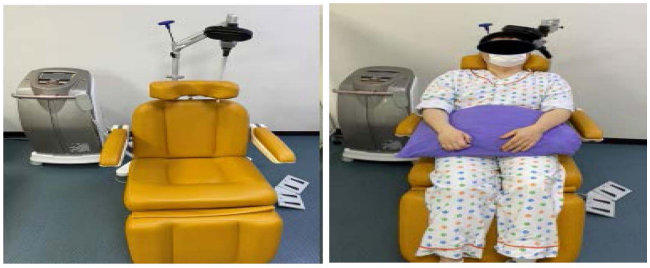
Each group received the same intervention three times a week for 30 min each session, and the study period was one month (February to March 2023). Before the intervention, the cerebral MEP amplitude and MEP latency were assessed, and then the intervention was applied for 4 weeks. The same post-evaluation was conducted after the completion of all interventions.

After receiving > 4 h of training from the person in charge to accurately utilize rTMS, which was used as a testing tool, a repeated intervention was conducted on two healthy participants to confirm reproducibility.

This study conducted a preliminary research survey from November to December 2022. After correcting and supplementing the problems, two patients hospitalized at O Hospital in Gyeonggi-do were selected, and a preliminary study was conducted for 2 weeks from January 2023. Subsequently, problems were corrected and supplemented during the research, and the intervention was conducted from February to March 2023. The statistics and results were summarized from March to April of the same year.

3.2.1. LF-rTMS (experimental group)

This study used ALTMS (REMED, Korea, 2018), which consists of a 70-mm 8-shaped coil, to apply LF-rTMS (Fig. 1a). After the patient was placed in a relaxed state on the machine chair, the head was fixed to the headrest, with both the upper arms and elbow joints extended and the wrist joints in a neutral position, the forearms prostrated, and the fingers extended (Fig. 1b). To evaluate the MEP threshold, a bandana with coordinates drawn from the participant's head was worn. The coordinates were connected from the nasion to the occipital point (inion), and a point was then created by intersecting the midsagittal and interaural lines on both sides. Based on this line, it is created by crossing lines in a checkerboard pattern at 1-cm intervals. The coil stimulator was positioned tangentially to the head of the uninjured cerebral hemisphere, with the handle facing backward and at an angle of 45° from the centerline. The cerebral cortex was stimulated on the undamaged side by activating the cerebral cortex and suppressing the cerebral cortex on the undamaged side when LF-rTMS was stimulated.



(a) (b)

Fig. 1. (Color online) (a) rTMS device (ALTMS, Remed, Korea). (b) Patient posture when applying rTMS.

The first dorsal interosseous (FDI) muscle was used as the target muscle for measuring MEPs in the hand (Fig. 2). To determine the location of the primary motor area (M1) of the FDI, stimulation was performed by slightly moving its position on the patient's scalp. To measure MEPs before study initiation, a silver electrode (silver-silver chloride electrode) was attached to the FDI, and a ground electrode was attached to the arm to measure electromyography values. Electromyography values were

Table 1. Treatment program for each group.

IFE-rTMS group (30 min)		IFE group (30 min)
1. Low frequency rTMS (20 min)	1 Hz, 1200 pulse, 120% MT	1. Specific activation of lumbricals 2. Specific activation of abductor digiti minimi 3. Thumb opposition 4. Index finger tapping movement
2. Individual finger exercise (10 min)	1. Specific activation of lumbricals 2. Specific activation of abductor digiti minimi 3. Thumb opposition 4. Index finger tapping movement	

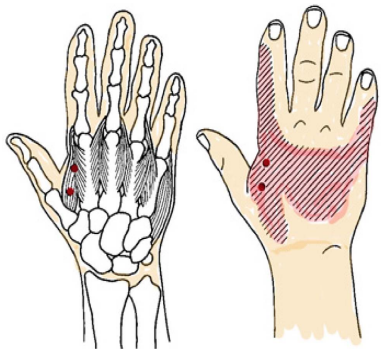


Fig. 2. (Color online) Attached surface electrodes: first dorsal interosseous (Electrode attachment area for MEP measurement).

recorded using the portable KEY POINT®.NET software, and the signal was amplified to 100 mV/div and then filtered to 2-10 KHz.

The point at which the largest MEP appeared in the recording potential of the FDI was considered the motor cortex area of the muscle. The resting motor threshold is defined as the minimum stimulation intensity at which a MEP of $\geq 50\ \mu V$ is recorded in at least 5 of 10 stimulations, and is performed on the uninjured side at an intensity of 120% of the motor threshold at 1200 pulses. To inhibit the cerebral motor cortex, a 1-Hz frequency was applied to the undamaged cerebral hemisphere for 20 min [28]. The patients participated three times a week for 4 weeks, 20 min per session, for a total of 12 sessions.

3.2.2. Individual finger exercise program (experimental group)

In this study, the individual finger exercise program was applied by referring to the finger intrinsic muscle treatment program proposed by Raine et al. in 2013, and modifying and supplementing it to suit the patient [29]. The total time is 10 min, and the individual finger

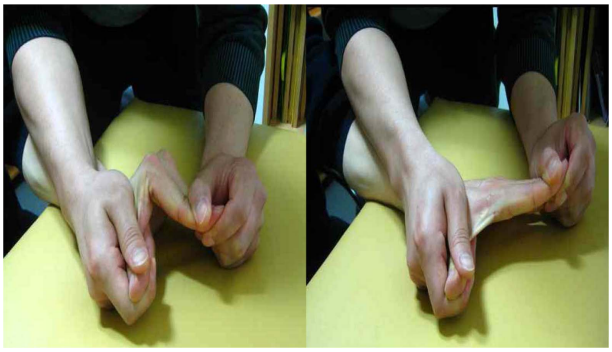


Fig. 3. (Color online) Specific activation of lumbricals (Training to stimulate the lumbricals muscle with a therapist).

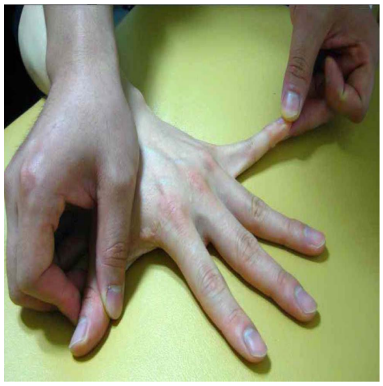


Fig. 4. (Color online) Specific activation of abductor digiti minimi (Little finger abduction exercises with a therapist to activate the abductor digiti minimi).

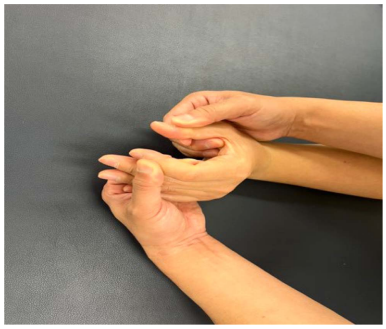


Fig. 5. (Color online) Thumb opposition (Training to place the subject's thumb opposition other fingers).

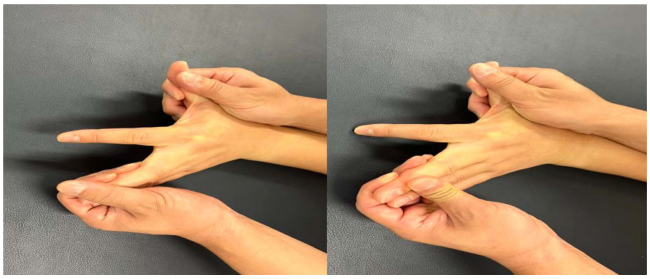


Fig. 6. (Color online) Index finger. This tapping movement.

exercise programs involved the specific activation of lumbricals (Fig. 3), specific activation of abductor digiti minimi (Fig. 4), thumb opposition (Fig. 5), and index finger. This tapping movement (Fig. 6) lasted for 10 min.

3.2.3. IFE group (control group)

The IFE group also underwent the same individual finger exercise program introduced previously. However, the individual finger exercises were performed for 30 min.

3.3. Assessment methods

3.3.1. Cerebral MEP amplitude and MEP latency evaluation

To measure the MEP amplitude and latency of the damaged cerebral cortex, the non-damaged cerebral cortex was stimulated using LF-rTMS to activate the cerebral cortex on the damaged side. The cerebral cortex on the non-damaged side was suppressed during LF-rTMS stimulation of the cerebral cortex on the non-damaged side.

The FDI muscle was used as the target muscle for measuring MEPs in the hand (Fig. 3). To determine the location of the primary motor area (M1) of the FDI, stimulation was performed by slightly moving its position on the patient's scalp. To measure MEPs before the study, a silver electrode (silver-silver chloride electrode) was attached to the FDI, and a ground electrode was attached to the arm to measure electromyography values. Electromyography values were recorded using portable the KEY POINT®.NET software, and the signal was amplified to 100 mV/div and then filtered to 2-10 kHz.

The point at which the largest MEP appeared in the recording potential of the FDI was considered the motor cortex area of the muscle. Resting motor threshold is defined as the minimum stimulation intensity at which MEPs of $\geq 50\,\mu V$ are recorded in at least 5 of 10 stimulations, and is the amplitude of MEPs stimulated with 120% of MEPs. The latency values were measured 15 times, the average value was determined [28], and two pre- and post-evaluations were conducted.

3.4. Statistical processing

The results of the collected data were statistically analyzed using the SPSS 18.0 program for Windows. Descriptive statistics and frequency analysis of the general characteristics of the study participants were conducted. The data collected were tested for normality, and all variables were normally distributed. A paired-samples t-test was performed to determine the differences in pre-, post-, and maintenance treatment effects within groups, and an independent-samples t-test was performed to compare between groups.

4. Results

4.1. General characteristics of the participants

The general characteristics of the study participants are listed in Table 2.

4.2. Comparison of effects before and after intervention within the IFE-rTMS group

A comparison of the change in MEP amplitude in the IFE-rTMS group revealed a significant increase from 0.131 mV before the intervention to 0.332 mV after the intervention ($p<0.001$). A significant decrease in MEP latency, ($p<0.001$) was observed before and after the intervention from 28.45 ms before the intervention to 24.95 ms after the intervention (Table 3).

4.3. Comparison before and after the experiment within the IFE group

Table 3. Comparison of results before and after with IFE-rTMS group.

	Pre-test	Post-test	*p*
	M±SD	M±SD	
MEP amplitude (mV)	0.131±1.72	0.332±2.10	.000***
MEP latency (ms)	28.45±4.24	24.95±2.10	.001***

Table 2. General characteristics of subjects.

Variables		IFE-rTMS group (N=10)	IFE group (N=10)
Gender	Male	6	5
	Female	4	5
Age		45.80±3.97	47.03±4.35
Lesion type	Hemorrhage	5	6
	Infarction	5	4
Lesion side	Right	4	5
	Left	6	5
Time from stroke to rehab (months)		26.35±4.56	23.52±6.72

M±SD
M: mean
SD: standard deviation
IFE-rTMS group : Individual finger exercise group after LF-rTMS group
IFE group : Individual finger exercise group

Table 4. Comparison of results before and after with IFE group.

	Pre-test	Post-test	*p*
	M±SD	M±SD	
MEP amplitude (mV)	0.125±0.10	0.302±2.45	.000***
MEP latency (ms)	30.82±2.93	28.88±3.54	.003**

Table 5. Comparison of results between the two groups.

	IFE-rTMS group (N=10)	IFE group (N=10)	*p*
	M±SD	M±SD	
MEP amplitude (mV)	0.201±0.38	0.177±2.35	.009**
MEP latency (ms)	-3.50±2.10	-1.94±0.61	.048*

In the IFE group, the change in MEP amplitude significantly increased ($p<0.001$) from 0.125 mV before the intervention to 0.302 mV after the intervention. Meanwhile, the change in MEP latency significantly decreased ($p<0.01$) before and after the intervention, from 30.82 ms in the pre-intervention evaluation to 28.88 ms in the post-intervention evaluation (Table 4).

4.4. Comparison before and after intervention between two groups

The changes before and after the intervention between the two groups revealed that the MEP amplitude was 0.201 mV in the IFE-rTMS group and 0.177 mV in the IFE group, which was significantly higher ($p<.01$) in the IFE-rTMS group before and after the intervention than in the IFE group. The MEP latency was −3.50 ms in the IFE-rTMS group and −1.94 ms in the IFE group, indicating a statistically significant decrease ($p<.05$) before and after intervention between the two groups (Table 5).

5. Discussion

Rehabilitation treatment for patients with brain disease involves helping them acquire premorbid skills and ways to compensate for their disabilities through learning and adaptation. Accordingly, various rehabilitation treatment methods have been proposed and applied to improve function through continuous learning of tasks appropriate to the patient. Existing rehabilitation treatment methods do not directly alter the brain, which is the cause of the lesion, and most methods seek to improve function by enhancing brain plasticity through appropriate external stimulation and changes in the environment [30, 31].

Recently, methods combining rTMS and exercise therapy have been applied in rehabilitation therapy. Kakuda et al. proved the effectiveness of upper extremity function in patients with stroke using 1-Hz LF-rTMS in combination with physical therapy. LF rTMS was performed for 20 min [32]. Additionally, Chang et al. applied 10 Hz high-frequency rTMS to patients with post-stroke hemiplegia to determine upper limb motor function and performed the intervention for >15 min [33].

Therefore, in this study, based on previous studies, individual finger movements after LF-rTMS were used to evaluate the amplitude and latency of MEPs in the motor cortex of the injured side of the cerebral cortex of patients with stroke.

A statistically significant increase in both the IFE-rTMS and IFE groups during pre- and post-intervention evaluations was observed. Therefore, the IFE-rTMS and IFE intervention methods effectively increased the amplitude of MEPs and decreased the latency time.

Further, when comparing the MEP amplitude and MEP latency between the two groups, the IFE-rTMS group demonstrated a statistically significant increase compared with the IFE group. These results may have a positive effect on transcallosal inhibition of TMS and individual finger movement. Transcerebral inhibition states that, under normal conditions, both cerebral hemispheres regulate and compete with each other. Corpus callosum inhibition occurs because the control and competition of the cerebral hemispheres inhibit each other through the corpus callosum in the cerebral medulla [34]. However, damage to one cerebral hemisphere, such as a stroke, causes an imbalance in cerebral cortical activity between the motor areas of both cerebral hemispheres, such that the damaged cerebral hemisphere receives strong inhibition from the non-damaged cerebral hemisphere, and the control of the body under the damaged cerebral hemisphere is affected, including exercise ability [35]. Based on this theory, in this study, LF-rTMS was applied to the normal cerebral hemisphere to reduce the normal cerebral cortical activity, which reversely activated the damaged cerebral hemisphere through transcortical cord inhibition, thereby improving MEPs. In addition, individual hand exercises are judged to have a more positive effect on improving cerebral motor cortex activity, as the fingers on the injured side participate in these exercises.

MEPs are related to the excitability of the cerebral cortex; if MEPs are not induced during appropriate magnetic stimulation, the nerve cells or nerve stems are dead or have a very high motor threshold [28, 36]. In this study, the amplitude of MEP ampulitude in the experimental group increased, which means that TMS stimulation excites several motor nerve pathways connected to the cerebral motor area on the damaged side of stroke

patients, thereby stimulating distal muscles through alpha motor neurons in the corresponding spinal cord related to hand movements. This means that it has been contracted. As a result, it activated muscle contraction on the injured side of the body. In addition, the research results showed that MEP latency was reduced as follows. The latency period expands the inhibition of cortical motor neurons and limits cell activity. This long latency period means that it takes a long time for muscle contraction. Therefore, as a result of this study, the decrease in MEP latency time means that the time for muscle contraction has become correspondingly shorter. Dafotakis et al. stated that the improvement in MEPs can positively indicate rehabilitation treatment, and when TMS was evaluated in the primary motor area of the cerebral cortex, motor induction was observed in the paralyzed upper limb muscles within 30 days after stroke. Patients with high MEPs have more positive functional recovery than those with low MEPs [37].

In many patients with stroke, the latency of MEPs is delayed owing to a decrease in the number of pyramidal neurons, increased temporal dispersion, and slow activity of pyramidal neuron groups in the lesioned motor and premotor cortices. This is attributed to the slow activity of the corticospinal tract of the supplementary motor cortex, slow reinnervation of the affected muscles, and contribution of slow-conducting nerve fibers from the normal cerebral hemisphere [38]. Therefore, in the results of this study, the fact that the latency of MEPs in the experimental group was further reduced compared to that in the control group is considered a predictive indicator that exercise ability can be improved by inducing MEPs more quickly. Traversa et al. have reported that a gradual decrease in latency was accompanied by clinical improvement and that patients with subacute stroke demonstrated a similar trend. Although whether this is attributed to individual differences is unclear, a shorter latency period can be expected in patients with chronic stroke with a relatively good functional status [39, 40].

To improve the motor function of many patients with brain damage, including current stroke, in this study, the treatment of hand movement and task application accompanied by rTMS improved motor ability by improving the amplitude of MEPs in the cerebral cortex on the damaged side. The results demonstrated reduced MEP latency, allowing the motor skills of the damaged cerebral hemisphere to be transferred more quickly to the relevant body parts, thereby improving the motor skills.

However, the limitations of this study include the difficulty of generalizing the results of the study due to the difficulty in recruiting more participants. Future studies should further investigate the failure to measure changes in actual motor function. Moreover, as no investigation has been conducted on the stimulation time and duration of post-cranial magnetic stimulation, research is needed to supplement these details, recruit more participants, and generalize the results of the study. Research on standards that can prove the effectiveness of TMS and the duration of its effect after the intervention is also considered necessary.

6. Conclusions

Individual finger movements after the main LF-rTMS indicated improved MEP amplitude in the cerebral cortex on the damaged side and decreased MEP latency.

Currently, various therapeutic methods are used to improve motor function in patients with brain damage diseases, including stroke. In particular, rTMS is used to improve brain plasticity in damaged brain function, as well as exercise therapy and tasks. The application of this treatment has attracted considerable attention. rTMS and individual finger movements can improve neurophysiological and kinematic functions and may be effective treatments for patients with brain damage and impaired motor functions.

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