NEURAL REGENERATION RESEARCH
December 2016, Volume 11, Issue 12
www.nrronline.org

RESEARCH ARTICLE

Does a combined intervention program of repetitive transcranial magnetic stimulation and intensive occupational therapy affect cognitive function in patients with post-stroke upper limb hemiparesis?

Takatoshi Hara[1,*], Masahiro Abo[1], Kiyohito Kakita[2], Takeshi Masuda[2], Ryunosuke Yamazaki[2]

1 Department of Rehabilitation Medicine, The Jikei University School of Medicine, Tokyo, Japan
2 Department of Rehabilitation Medicine, Kyoto Ohara Memorial Hospital, Kyoto, Japan

How to cite this article: *Hara T, Abo M, Kakita K, Masuda T, Yamazaki R (2016) Does a combined intervention program of repetitive transcranial magnetic stimulation and intensive occupational therapy affect cognitive function in patients with post-stroke upper limb hemiparesis? Neural Regen Res 11(12):1932-1939.*

Abstract

Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) to the contralesional hemisphere and intensive occupational therapy (iOT) have been shown to contribute to a significant improvement in upper limb hemiparesis in patients with chronic stroke. However, the effect of the combined intervention program of LF-rTMS and iOT on cognitive function is unknown. We retrospectively investigated whether the combined treatment influence patient's Trail-Making Test part B (TMT-B) performance, which is a group of easy and inexpensive neuropsychological tests that evaluate several cognitive functions. Twenty-five patients received 11 sessions of LF-rTMS to the contralesional hemisphere and 2 sessions of iOT per day over 15 successive days. Patients with right- and left-sided hemiparesis demonstrated significant improvements in upper limb motor function following the combined intervention program. Only patients with right-sided hemiparesis exhibited improved TMT-B performance following the combined intervention program, and there was a significant negative correlation between Fugl-Meyer Assessment scale total score change and TMT-B performance. The results indicate the possibility that LF-rTMS to the contralesional hemisphere combined with iOT improves the upper limb motor function and cognitive function of patients with right-sided hemiparesis. However, further studies are necessary to elucidate the mechanism of improved cognitive function.

Key Words: *nerve regeneration; stroke; repetitive transcranial magnetic stimulation; Trail-Making Test; cognitive function; occupational therapy; neural regeneration*

Correspondence to:
Takatoshi Hara, M.D.,
t_hara1019@jikei.ac.jp.

doi: *10.4103/1673-5374.197134*

Accepted: *2016-11-30*

Introduction

Upper limb hemiparesis is reported to be observed in 55–75% of post-stroke patients, and affects the patient's activities of daily living and quality of life (Nichols-Larsen et al., 2005; Wolf et al., 2006). Duncan et al. (1992) reported that dramatic recovery of motor function was completed by 1month post-stroke, and that recovery often plateaued by 6 months. In recent years, repetitive transcranial magnetic stimulation (rTMS) has attracted attention as a treatment technique for the sequelae of stroke. It is a non-invasive, painless method to stimulate regions of the cerebral cortex, in which a figure-8 or a round coil converts electrical current into a rapidly variable magnetic field that is orthogonal to the current. Eddy currents generated by the changes of the magnetic field directly affect neurons (Barker, 1999). In addition, it has been known that different stimulation frequencies have different effects on the activities of the cerebral cortex, with high-frequency (> 5 Hz) stimulation facilitating local neuronal excitability and low-frequency (< 1 Hz) stimulation showing inhibitory effects (Lefaucheur, 2006; Butler and Wolf, 2007). Low-frequency rTMS (LF-rTMS) aims at increasing the excitability of the ipsilesional hemisphere by exerting its effects on the disrupted interhemispheric inhibition following stroke and thereby providing inhibitory stimulation to the contralesional hemisphere. Meta-analyses of rTMS in patients with stroke indicate that LF-rTMS is recommended for stroke patients in the chronic phase (> 6 months post-stroke), showing a strong possibility of a significant improvement of their upper limb function (Hsu et al., 2012; Le et al., 2014). In the past, our research group implemented a 15-day treatment protocol consisting of LF-rTMS and an intensive individualized rehabilitation program for patients with upper limb hemiparesis following stroke, and demonstrated a significant improvement of upper limb hemiparesis (Kakuda et al., 2011, 2012, 2016). Furthermore, we investigated the effects of our treatment protocol on brain activity and demonstrated a significant increase in the fMRI laterality index, indicating increased neuronal activity in the ipsilesional hemisphere (Yamada et al., 2013). Our single photon emission computed tomography (SPECT) study also demonstrated a significant decrease in perfusion in the middle frontal gyrus (Brodmann area; BA6), precentralgyrus (BA4), and post central gyrus (BA3) of the contralesional hemisphere, as well as an increased perfusion in the insula (BA13) and precentral gyrus (BA44) of the ipsilesional hemisphere (Hara et al., 2013). Thus, we demonstrated changes in brain activity between pre- and post-treatment that combined LF-rTMS and an intensive occupational therapy (iOT) program.

In recent studies, rTMS was used not only in treating upper limb hemiparesis after stroke, but also for other conditions, including neurological and psychiatric disorders, pain, and Parkinson's disease (Lefaucheur et al., 2014). Furthermore, some studies conducted neuropsychological examinations at the time of rTMS to evaluate its effect on cognitive function (Nardone et al., 2014; Drumond Marra et al., 2015). One study reported an improvement in cognitive function following rTMS in patients with mild cognitive impairment (Nardone et al., 2014). Drumond Marra et al. (2015) reported an improved performance on the Rivermead Behavioral Memory Test following high-frequency rTMS (HF-rTMS) to the left dorsolateral prefrontal cortex (DLPFC).

Furthermore, the effects of rTMS on cognitive function in addition to motor disorders, aphasia, and affective disorders have been attracting attention (Lefaucheur et al., 2014; Nardone et al., 2014; Drumond Marra et al., 2015). One study reported an improvement in Trail-Making Test part B (TMT-B) performance by HF-rTMS, while another study reported a lack of significant improvement relative to a control group (Moser et al., 2002; Mittrach et al., 2010). However, few studies have investigated the effects of LF-rTMS on cognitive function. As described earlier, LF-rTMS exerts an inhibitory stimulation to the side of administration and is considered to affect the contralateral cerebral cortices *via* a modulation of interhemispheric inhibition. Therefore, LF-rTMS possibly affects a broader region than that affected by HF-rTMS. Meta-analyses of rTMS in patients with stroke indicate that LF-rTMS is recommended for stroke patients in the chronic phase (> 6 months post-stroke).

Although previous studies indicate a possibility of positive effects of rTMS on cognitive function; however, to the best of our knowledge, there has been no report describing the effect of a combined intervention program of LF-rTMS and intensive occupational therapy (iOT) on cognitive function in post-stroke patients. Therefore, the present study aimed to explore the therapeutic effect of the combined intervention program on patients with post-stroke upper limb hemiparesis.

Subjects and Methods

Subjects and study protocol

Thirty-two patients with post-stroke unilateral upper limb hemiparesis who were admitted to Kyoto Ohara Memorial Hospital, Japan between January 2014 and March 2015 were included in this retrospective study. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (UMIN-ID; 000023192). **Figure 1** shows flow chart of the study.

Thirty-two patients met the following inclusion criteria adopted from Kakuda et al. (2010): (1) Brunnstrom stage 3–5 for hand-fingers (ability, at least subjectively, to flex all the fingers of the affected upper limb in full range of motion); (2) age between 18–90 years; (3) a duration between the onset of stroke and intervention longer than 6 months; (4) history of a single stroke only (no bilateral cerebrovascular lesion); (5) independent indoor activities of daily living; (6) clinical confirmation of the plateau state, representing no increase on the Fugl-Meyer Assessment (FMA) score, an internationally established measure with high utility and validity (Gladstone et al., 2002) by an occupational therapist from the institution in last 3 months; (7) no active physical or mental illness requiring medical management; (8) no recent history of seizure (within 1 year preceding the intervention); (9) no documented epileptic discharge on pretreatment electroencephalogram; (10) no current use of antiepileptic medications for the prevention of seizure; and (11) no pathological conditions known to be contraindications for rTMS in the guidelines suggested by Wassermann (1998). **Table 1** shows the clinical characteristics of the participants. There were no statistically significant differences in age, time from the stroke onset to the current intervention, or TMT performance between the patients with right-sided and left-sided hemiparesis ($P > 0.05$). Prior to participation, the attending physicians fully explained the treatment protocol to the patients and all patients provided written informed consent. In addition, the current study was approved by the institutional review boards of Tokyo Jikei University School of Medicine (approval No. 19-085) and Kyoto Ohara Memorial Hospital (approval No. 12001). The patients were assigned to left LF-rTMS and right LF-rTMS groups.

TMT

TMT is a group of easy and inexpensive neuropsychological tests to evaluate several cognitive functions that consists of two parts, TMT-A and TMT-B. TMT-A requires that subjects draw lines sequentially connecting circles marked with numbers (1 to 25) that are randomly distributed on a sheet of paper. In TMT-B, subjects have to draw lines sequentially connecting circles marked alternately with numbers and letters (for examples, 1-A, 2-B…M-13). TMA-A reflects attention, visual search, and working memory (Crowe, 1998), while the TMT-B reflects executive processes such as cognitive set-shifting (Sánchez-Cubilloet al., 2009; Jacobson et al., 2011). Studies have demonstrated that brain regions activated during TMT-A and TMT-B are slightly different (Zakzanis et al., 2005). In particular, in TMT-B, a test that is considered to measure cognitive set-shifting, the left hemisphere has been shown to be more activated than the right hemisphere. TMT is an instrument that is administered to detect primarily attention disorders, and has been shown to have high utility and validity internationally (Lezak, 1983). In Japan, TMT has been used increasingly in clinical settings, and has been demonstrated to provide results that are consistent with other tests of attention (Toyokura, 2008). In this study, we used TMT primarily because administering a time consuming instrument to assess cognitive function was not possible since the patients' purpose of hospital admission was to improve upper limb function. In addition, using TMT was to consider a possible burden on patients by using an extensive or larger battery of tests.

Similar to the upper limb motor function evaluation, the TMT was administered at admission and at discharge. The location and the desk that were used in the upper limb motor function evaluation were used for the pencil-paper TMT task. During the test trials of the TMT, the examiner corrected any participant errors immediately and recorded times and numbers of errors in each part of the task. The patients used their unaffected upper limb to perform the TMT. No significant differences had been reported in the completion times for the right and left hands. Therefore, cognitive function was well reflected on the results of the TMT performed with the patient's unaffected hand, even when it happened to be their non-dominant hand (Toyokura et al., 2003a). Furthermore, the TMT difference score, calculated as TMT-A subtracted from TMT-B (B–A), is considered to reflect the removal of the speed component of the TMT (Periáñez et al., 2007). Therefore, we calculated this B–A difference score as well. The same occupational therapist evaluated the upper limb function and performed TMT tests at admission and discharge.

Twenty-five of the 32 patients completed both the TMT-A and TMT-B tests. The seven patients excluded were only able to complete the TMT-A test. One of those seven patients was subsequently able to complete the TMT-B test at discharge, but we continued to exclude this patient. In TMT, not only TMT-A and TMT-B scores, but also B–A difference score are clinically important. Therefore, those patients who did not complete both TMT-A and TMT-B tests were excluded (Toyokura, 2008).

Application of rTMS

LF-rTMS was applied using a 70-mm figure-8 coil and MagProR30 stimulator (MagVenture, Farum, Denmark). According to the current safety recommendations, 1-Hz LF-rTMS was applied to the contralesional hemisphere over the primary motor area (Wassermann, 1998). Each LF-rTMS session consisted of 2,400 pulses, lasting 40 minutes. The optimal site of stimulation on the skull was defined as the location where the largest motor evoked potentials in the first dorsal interosseous muscle of the unaffected upper limb were elicited on surface electromyography. The resting motor threshold (MT) of this muscle of the unaffected upper limb was defined as the minimum stimulus intensity that produced a minimal motor evoked response of the muscle at rest. The intensity of stimulation was then set at 90% of the measured resting MT. LF-rTMS to patients with hemiparesis in the chronic stage of stroke is expected to reduce interhemispheric inhibition to the compensating regions, as well as facilitate neuronal activity in the compensating regions (Hara et al., 2013). Therefore, we expected that an improvement in cognitive function may be induced in addition to an improvement in upper limb function when the rTMS exerted its effects on a larger area of the ipsilesional hemisphere. The first reason we used LF-rTMS was the reduced risk of seizures compared to HF-rTMS (Wassermann, 1998). The second reason was that HF-rTMS is considered to impact only the region directly under the stimulation, and the impact on a broader cerebral network is small (Sale et al., 2015). Third, the effects of LF-rTMS were expected to be extensive, including the contralateral homologous regions of the target regions (Grefkes et al., 2010, 2011). Furthermore, the "online interference approach" of TMS has been utilized in healthy individuals to examine cognitive function. This approach involves TMS stimulation at a specific region of the brain during a specific time while the examinee is performing a task. Then, the examinee's task performance and functional brain image data are evaluated (Rossini et al., 2015).

Schedule of 15-day protocol of combined LF-rTMS and iOT

LF-rTMS therapy and iOT program were implemented with the schedule shown in **Table 2**. Eleven sessions of LF-rTMS therapy, one session per day, excluding the days of admission, discharge, and Sunday, were administered. Two sessions of iOT were performed each day, excluding the days of admission, discharge, and Sunday, resulting in 22 sessions over 15 successive days. The iOT program consisted of 60 minutes of individualized iOT and 60 minutes of self-training. In individual iOT sessions, the patient and the occupational therapist met one on one. In addition, to minimize potential training differences among occupational therapists, two occupational therapists, who had a thorough knowledge of this protocol and had experience in treating more than 50 patients using the current protocol, administered the iOT intervention for the current study. Furthermore, the iOT program was administered with the aim of improving upper limb function. Individual iOT sessions consisted of shaping techniques and repetitive task practice. They engaged in a training program that took into consideration the patient's degree of upper limb hemiparesis, needs, and living conditions, which was assessed at the time of an intake interview by the physician. Training assignments during the self-training session were based on the materials covered during the therapist-led individualized therapy sessions. A booklet was created for each patient containing instructions and tips for training, and the patient utilized the booklet to engage in self-training without help from the therapist. The evaluations of upper limb motor function were conducted on the days of admission and discharge. In the current study, the patients used their unaffected upper limb to perform TMT. To minimize the effect of the iOT sessions on the unaffected limb, the iOT training program did not include movement training that involved both upper limbs.

Evaluation of motor function

Upper limb items from the FMA task, completion time of the Wolf Motor Function Test (WMFT) (Morris et al., 2001), and Action Research Arm Test (ARAT) (Chen et al., 2012) were used for this evaluation. Shorter WMFT completion time indicates better motor function. Greater FMA and ARAT scores represent better motor function. Shorter TMT time indicates better cognitive function. For the FMA, we used 33 items (maximum 66 points) pertaining to upper limb function, including shoulder, elbow, forearm, wrist, and hand. Due to its large variability, we naturally log-transformed the WMFT task completion time. A pre- vs. post-treatment difference score was calculated for the TMT. TMT completion time at admission was subtracted from the completion time at discharge. Similarly, upper limb motor function assessment scores at admission (pre-treatment) were subtracted from those at discharge (post-treatment).

Statistical analysis

Mann-Whitney *U* test was used to compare the baseline data between patients with right-sided hemiparesis (right hemisphere LF-rTMS) and left -sided hemiparesis (left hemisphere LF-rTMS). Wilcoxon signed-rank test was used to compare the pre- and post-treatment FMA scores. Paired *t*-tests were used to compare pre- and post-treatment WMFT completion times, ARAT, and TMT scores. Spearman's correlation coefficients were calculated to analyze the relationship between TMT performance and upper limb motor function scores. Bonferroni corrections were used to correct for multiple comparisons. All analyses were performed using SPSS 21.0 software (IBM, Armonk, NY, USA), with an alpha of 0.05 (two-sided test).

Results

Upper limb motor functions

As shown in **Table 3**, in patients with right-sided hemiparesis (right LF-rTMS), significant increases were observed in FMA categories A–C scores ($P < 0.05$), but not in FMA category D. The WMFT or ARAT completion time, was significantly shortened, or increased, after treatment than before treatment (both $P < 0.05$). In patients with left-sided hemiparesis (left LF-rTMS), significant increases were observed in FMA categories A and C scores (both $P < 0.05$) and in ARAT completion time ($P < 0.05$).

TMT

In the right LF-rTMS group, TMT-B performance significantly improved after treatment than that before treatment ($P < 0.05$). In the left LF-rTMS group, there was no significant difference in TMT-A, TMT-B or B–A difference values between pre- and post-treatment ($P > 0.05$). However, in the right LF-rTMS group, significant correlation was observed between pre- *vs*. post-treatment change in FMA total score and pre- *vs*. post-treatment change in TMT-B value ($r = –0.651$, $P = 0.009$, $R^2 = 0.263$; **Figure 2**).

Discussion

In the current study, we administered LF-rTMS and iOT to patients with post-stroke upper limb hemiparesis. Similar to our previous studies (Kakuda et al., 2011, 2012, 2016), we demonstrated a significant improvement in upper limb motor function following the combined strategy. In addition, we added a cognitive function assessment and observed a significant improvement in TMT-B performance. Pre- *vs*. post-treatment TMT-B score change was associated with pre- *vs*. post-treatment FMA total score change in patients with right-sided hemiparesis.

Moser et al. (2002) administered 20 Hz rTMS over the left middle frontal gyrus of individuals with refractory depression and reported a significant improvement in TMT-B performance. Although no improvement in TMT was observed in patients with schizophrenia who received 10 Hz rTMS over the left prefrontal cortex (PFC), a slightly improved performance was observed in these patients on the Wisconsin Card Sorting Test (Mittrach et al., 2010). Evidence suggests that HF-rTMS to the left DLPFC or LF-rTMS to the right DLPFC is effective in the treatment of depression (Lefaucheur, 2006). An explanation for this may be that activation of the left DLPFC *via* transcallosal pathways contributes to the improvement of depression. Also, stimulation to the ipsilesional hemisphere in the acute period and to the contralesional side in the chronic period was effective for improving upper limb motor function in post-stroke patients (Hsu et al., 2012), presumably due to excitation of the ipsilesional hemisphere by rTMS or to a transcallosal-pathway contribution.

It remains unclear regarding which side of rTMS contributes to improvement in cognitive function. Eliasova et al. (2014) reported significant improvement in both TMT-A and TMT-B in patients with Alzheimer's disease or mild cognitive impairment who received LF-rTMS to the right inferior frontal gyrus. The optimal administration site and frequency of rTMS and the hemisphere administered may be different in patients with different disorders, because rTMS administration at different sites and frequencies provide positive effects on cognitive function. The optimal parameters of rTMS used for different disorders need to be further investigated.

Several studies support our findings that activation of the left hemisphere possibly leads to an improvement in TMT-B performance in patients with right-sided hemiparesis. fMRI studies reported that activation of the left frontal and temporal lobes provided greater improvement in TMT-B performance than in TMT-A performance (Moll et al., 2002; Zakzanis et al., 2005). Furthermore, using functional near-infrared spectroscopy, Fujiki et al. (2013) reported that activation with left-hemisphere dominance was observed with an improvement in TMT-B performance in individuals with schizophrenia. All studies cited here reported left PFC involvement during the TMT-B perfor-

Table 1 Baseline data of the included patients

	All patients (n = 25)	Right-sided hemiparesis (right LF-rTMS) (n = 15)	Left-sided hemiparesis (left LF-rTMS) (n = 10)
Age (year)	61.8±14.1	58.8±15.8	66.3±10.2
Gender (male /female, n)	15/10	9/6	6/4
Type of stroke			
Cerebral infarction (n)	11	8	3
Intracerebral hemorrhage (n)	14	7	7
Brunnstrom stage (median)			
Upper limb	5	4	5
Finger	4	4	4
Time between onset and treatment (month)	45.9±48.5	49.8±59.4	40.2±27.2
TMT-A (second)	58.0±38.4	64.8±46.2	47.7±20.6
TMT-B (second)	138.3±64.9	149.7±78.1	121.3±34.7
B–A	80.3±38.3	84.9±46.6	73.5±21.1

Continuous variables are expressed as the mean ± SD except for Brunnstrom stage. TMT-A: The Trail-Making Test part A; TMT-B: The Trail-Making Test part B; B–A: completion time for TMT-B minus completion time for TMT-A; LF-rTMS: low-frequency repetitive transcranial magnetic stimulation.

Table 2 Schedule of 15-day protocol of combined LF-rTMS and iOT in one patient admitted on Wednesday

	Wednesday	Thursday–Saturday	Sunday	Monday–Saturday	Sunday	Monday–Tuesday	Wednesday
Morning	Admission	LF-rTMS (40 minutes) One to one iOT training (60 minutes) Self-training (60 minutes)	No treatment	LF-rTMS (40 minutes) One to one iOT training (60 minutes) Self-training (60 minutes)	No treatment	LF-rTMS (40 minutes) One to one iOT training (60 minutes) Self-training (60 minutes)	Post-treatment evaluation
Afternoon	Pre-treatment evaluation	One to one iOT training (60 minutes) Self-training (60 minutes)	No treatment	One to one iOT training (60 minutes) Self-training (60 minutes)	No treatment	One to one iOT training (60 minutes) Self-training (60 minutes)	Discharge

LF-rTMS: Low-frequency repetitive transcranial magnetic stimulation; iOT: intensive occupational therapy.

Table 3 Upper limb motor function assessment scores and the TMT values pre- and post-treatment

	Right-sided hemiparesis (right LF-rTMS)		Left-sided hemiparesis (left LF-rTMS)	
Assessment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FMA				
Total score	34.4±14.6	41.6±12.9*	47.1±9.5	53.3±7.5*
Category A	22.6±7.3	26.3±5.9*	28.5±3.3	31.0±3.2*
Category B	3.4±4.4	4.6±4.0*	6.7±3.2	7.2±3.0
Category C	7.1±3.6	9.3±3.6*	9.6±4.1	12.0±2.3*
Category D	1.2±1.8	1.6±1.8	2.3±1.7	3.1±1.85
WMFT (second)	2.6±0.45	2.5±0.45*	2.1±0.45	1.96±0.45
ARAT (second)	18.4±13.1	22.3±15.7*	33.6±13.8	37.1±16.0*
TMT-A (second)	64.8±46.2	53.4±32.4	47.7±20.6	42.5±15.1
TMT-B (second)	149.7±78.1	117.6±58.7*	121.3±34.7	129.6±54.1
B–A (second)	84.9±46.6	64.1±36.9	73.5±21.1	87.0±45.9

All data are expressed as the mean ± SD. FMA: Fugl-Meyer Assessment; WMFT: Wolf Motor Function Test; LF-rTMS: low-frequency repetitive transcranial magnetic stimulation; ARAT: Action Research Arm Test; TMT-A: The Trail Making Test part A; TMT-B: The Trail Making Test part B; B–A: completion time for TMT-B minus completion time for TMT-A. *P < 0.05, *vs*. pre-treatment. Wilcoxon signed-rank test was used to compare the pre- and post-treatment FMA scores. Paired t-tests were used to compare pre- and post-treatment WMFT completion time, ARAT, and TMT values.

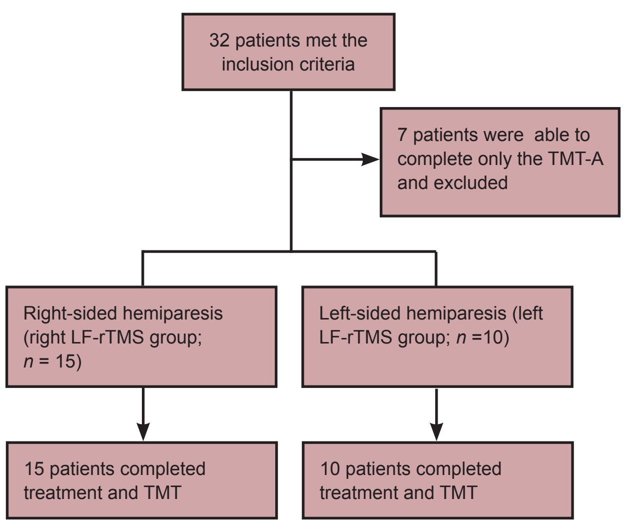

Figure 1 Flow chart of the study.
TMT-A: Trail-Making Test part A; LF-rTMS: low-frequency repetitive transcranial magnetic stimulation.

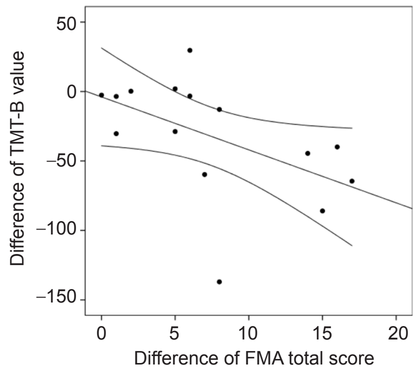

Figure 2 Relationship between pre- *vs*. post-treatment FMA total score change and pre- *vs*. post-treatment TMT-B value change.
There was a significant negative correlation between pre- *vs*. post-treatment FMA total score change and pre- *vs*. post-treatment TMT-B score change (r = -0.651, P = 0.009, R^2 = 0.263). The straight line is the regression line, and the curved lines represent 95% confidence intervals for the regression line. Spearman's correlation coefficients were used.

mance; however, we did not conduct an imaging examination in the current study, which should be accomplished in our future studies. Therefore, we believe that future investigations should include paired-pulse TMS and functional brain imaging.

From the standpoint of cognitive function, TMT-B is considered to reflect executive function or set-shifting abilities. TMT is considered to be related in particular to attention among various cognitive functions. Generally, attention is classified into "generalized attention" and "directed attention," with the former considered to consist of three components, including (1) select, (2) sustain, and (3) shift. However, unilateral spatial neglect is suggested to occur when shift is disturbed, and TMT-B is suggested to assess an aspect of "shift" (Mirskyet al., 1991). Studies on the localization of attention indicates that the "selection" component is localized to the inferior parietal lobe and temporal lobe, the "sustain" component is localized to the tegmentum, reticular formation of the mid brain and pons, and thalamus, and the "shift" component is localized to DLPFC and cingulate gyrus. For unilateral spatial neglect that is caused by disrupted "directed attention", a mechanism of directional deficits has been proposed (Weintraub, 1989). According to this mechanism, unilateral spatial neglect occurs often due to an insult to the left hemisphere because the left hemisphere is only attending to the right-hand space of the patient, while the right hemisphere is attending to both sides. However, the lateralization of "generalized attention" is not fully understood. In the current study, TMT-B performance improved following the combined LF-rTMS and iOT intervention in patients with right-sided hemiparesis. This suggests that our treatment protocol not only improved upper limb hemiparesis, but also executive function and set shifting abilities in patients with right-sided upper limb hemiparesis. A previous study suggested that the time required to complete TMT consists of two elements, including "motor time" when the examinee moves the pen and "cognitive time" when the examinee correctly selects and detects targets (Toyokura, 2003b). According to this study, "motor time" has little individual variability and has little impact on TMT scores. However, "cognitive time" has a larger individual variability, and TMT scores are mostly determined by this element. In the current study, rTMS was administered to the motor region of the contralesional hemisphere, and previous studies suggest that this is unlikely to affect upper limb function of the unaffected side (Kakuda et al., 2010). In addition, our iOT aimed to improve upper limb function of the affected side, but not the unaffected limb. Therefore, it is unlikely that the intervention improved the "motor time" of the unaffected limb. Rather, the intervention likely impacted the "cognitive time" and improved the TMT-B performance of patients receiving right LF-rTMS.

The PFC, a region where brain activation was observed in previous studies of rTMS and TMT, was not the target of stimulation in the current study. We observed changes in TMT value, suggesting a neural network involving both the primary motor cortex and the PFC may be involved in the performance of the TMT.

Focal stimulation by rTMS is reported not only to change the neuronal connectivity between the stimulation site and its homologous region, but also to affect regions far from the stimulation site (Grefkes et al., 2010). Another fMRI study with a similar method suggested that network remodeling of the whole brain, rather than excitatory changes in individual motor regions, may be responsible for the positive effects of rTMS (Grefkes et al., 2011). Thus, it is possible that our treatment protocol not only affected the neuronal network between the motor cortices of the two hemispheres but also the PFC that has some connectivity with the motor cortices. Our future studies should include functional neuroimaging, such as fMRI and SPECT, pre- and post-treatment along with the TMT, and investigate whether changes in brain activation and TMT performance are associated. Reports using rTMS to improve cognitive functioning are scarce. We hope to consider adding neuropsychological instruments other than the TMT to assess such changes.

The set-shifting function is thought to be left-hemisphere dominant, and LF-rTMS to the right motor region combined with iOT affected a broad region *via* neural networks. In particular, it is possible that plasticity of the left hemisphere improves due to the resolution of imbalance of interhemispheric inhibition that occurs in the chronic stage of stroke. Future studies should investigate this potential mechanism that is suggested by the current results.

The current study has some limitations. First, it is an intervention study without a control group. The current study is a retrospective investigation and only suggests that LF-rTMS to the right hemisphere combined with iOT improves TMT-B performance. Future studies should also include a sham stimulation group or iOT alone for comparison. Second, the rehabilitation program that the patients received is not uniform across the patients. Because the rehabilitation program is tailored to each patient's needs, it is possible that the effect it has on cognitive function is also not uniform. Because it is very difficult to have a uniform training content, we should consider having a uniform training goal in future studies.Third, we performed assessments only at admission and discharge. In general, follow-up evaluations are necessary to evaluate the duration of the effects of intervention. However, we were unable to perform follow up evaluations in the current study due to social factors. In future investigations using the current protocol, we hope to perform follow up evaluations 1 and 3 months after discharge to evaluate the continued effects of treatment and to administer additional neuropsychological measures.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

Author contributions: *TH and MA conceived and designed the study. TH, MA, KK, TM and RY performed the study. TH analyzed the data and wrote the paper. All authors approved the final version of this paper for publication.*

Conflicts of interest: *None declared.*

Plagiarism check: *This paper was screened twice using CrossCheck to verify originality before publication.*

Peer review: *This paper was double-blinded and stringently reviewed by international expert reviewers.*

References

Barker AT (1999) The history and basic principles of magnetic nerve stimulation. Electroencephalogr Clin Neurophysiol Suppl 51:3-21.

Butler AJ, Wolf SL (2007) Putting the brain on the map: use of transcranial magnetic stimulation to assess and induce cortical plasticity of upper-extremity movement. Phys Ther 87:719-736.

Chen HF, Lin KC, Wu CY, Chen CL (2012) Rasch validation and predictive validity of the action research arm test in patients receiving stroke rehabilitation. Arch Phys Med Rehabil 93:1039-1045.

Crowe SF (1998) The differential contribution of mental tracking, cognitive flexibility, visual search, and motor speed to performance on parts A and B of the Trail Making Test. J Clin Psychol 54:585-591.

Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, Lancelote Alberto R, Boura Bellini B, Alves Fernandes da Silva A, Tortella G, Ciampi de Andrade D, Teixeira MJ, Forlenza OV, Marcolin MA (2015) Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. Behav Neurol 2015:287843.

Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J (1992) Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke 23:1084-1089.

Eliasova I, Anderkova L, Marecek R, Rektorova I (2014) Non-invasive brain stimulation of the right inferior frontal gyrus may improve attention in early Alzheimer's disease: a pilot study. J Neurol Sci 346:318-322.

Fujiki R, Morita K, Sato M, Kamada Y, Kato Y, Inoue M, Shoji Y, Uchimura N (2013) Reduced prefrontal cortex activation using the Trail Making Test in schizophrenia. Neuropsychiatr Dis Treat 9:675-685.

Gladstone DJ, Danells CJ, Black SE (2002) The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair 16:232-240.

Grefkes C, Fink GR (2011) Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain 134:1264-1276.

Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR (2010) Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 50:233-342.

Hara T, KakudaW, Kobayashi K, MomosakiR, NiimiM, AboM (2013) Regional cerebral blood flow (rCBF) after low-frequency repetitive transcranial magnetic stimulation (rTMS) combined with intensive occupational therapy for upper limb hemiplegia after stroke: a study using single photon emission computed tomography. Jpn J Rehabil Med 50:36-42.

Hsu WY, Cheng CH, Liao KK, Lee IH, Lin YY (2012) Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. Stroke 43:1849-1857.

Jacobson SC, Blanchard M, Connolly CC, Cannon M, Garavan H (2011) An fMRI investigation of a novel analogue to the Trail-Making Test. Brain Cogn 77:60-70.

Kakuda W, Abo M, Kobayashi K, Momosaki R, Yokoi A, Fukuda A, Ishikawa A, Ito H, Tominaga A (2010) Low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy for poststroke patients with upper limb hemiparesis: preliminary study of a 15-day protocol. Int J Rehabil Res 33:339-345.

Kakuda W, Abo M, Kobayashi K, Takagishi T, Momosaki R, Yokoi A, Fukuda A, Ito H, Tominaga A (2011) Baseline severity of upper limb hemiparesis influences the outcome of low-frequency rTMS combined with intensive occupational therapy in patients who have had a stroke. PM R 3:516-522.

Kakuda W, Abo M, Shimizu M, Sasanuma J, Okamoto T, Yokoi A, Taguchi K, Mitani S, Harashima H, Urushidani N, Urashima M; NEURO Investigators (2012) A multi-center study on low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis in post-stroke patients. J Neuroeng Rehabil 9:4.

Kakuda W, Abo M, Sasanuma J, Shimizu M, Okamoto T, Kimura C, Hara H (2016) Combination protocol of low-frequency rTMS and intensive occupational therapy for post-stroke upper limb hemiparesis: a 6-year experience of more than 1700 Japanese patients. Transl Stroke Res 7:172-179.

Le Q, Qu Y, Tao Y, Zhu S (2014) Effects of repetitive transcranial magnetic stimulation on hand function recovery and excitability of the motor cortex after stroke: a meta-analysis. Am J Phys Med Rehabil 93:422-430.

Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, et al. (2014) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125:2150-2206.

Lefaucheur JP (2006) Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS). Neurophysiol Clin 36:105-115.
Lezak MD (1983) Neuropsycological Assessment. 2nd Ed., Oxford University Press, New York.
Mirsky AF, Anthony BJ, Duncan CC, Ahearn MB, Kellam SG (1991) Analysis of the elements of attention: a neuropsychological approach. Neuropsychol Rev 2:109-145.
Mittrach M, Thünker J, Winterer G, Agelink MW, Regenbrecht G, Arends M, Mobascher A, Kim SJ, Wölwer W, Brinkmeyer J, Gaebel W, Cordes J (2010) The tolerability of rTMS treatment in schizophrenia with respect to cognitive function. Pharmacopsychiatry 43:110-117.
Moll J, de Oliveira-Souza R, Moll FT, Bramati IE, Andreiuolo PA (2002) The cerebral correlates of set-shifting: an fMRI study of the trail making test. Arq Neuropsiquiatr 60:900-905.
Morris DM, Uswatte G, Crago JE, Cook EW, 3rd, Taub E (2001) The reliability of the wolf motor function test for assessing upper extremity function after stroke. Arch Phys Med Rehabil 82:750-755.
Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG (2002) Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 58:1288-1290.
Nardone R, Tezzon F, Höller Y, Golaszewski S, Trinka E, Brigo F (2014) Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease. Acta Neurol Scand 129:351-366.
Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S (2005) Factors influencing stroke survivors' quality of life during subacute recovery. Stroke 36:1480-1484.
Periáñez JA, Ríos-Lago M, Rodríguez-Sánchez JM, Adrover-Roig D, Sánchez-Cubillo I, Crespo-Facorro B, Quemada JI, Barceló F (2007) Trail Making Test in traumatic brain injury, schizophrenia, and normal ageing: Sample comparisons and normative data. Arch Clin Neuropsychol 22:433-447.
Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, et al. (2015) Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 126:1071-1107.
Sale MV, Mattingley JB, Zalesky A, Cocchi L (2015) Imaging human brain networks to improve the clinical efficacy of non-invasive brain stimulation. Neurosci Biobehav Rev 57:187-198.
Sánchez-Cubillo I, Periáñez JA, Adrover-Roig D, Rodríguez-Sánchez JM, Ríos-Lago M, Tirapu J, Barceló F (2009) Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc 15:438-450.
Toyokura M (2008) Clinical attributes of attentional impairment. High Brain Funct Res 28:320-328.
Toyokura M, Sawatari M, Nishimura Y, Ishida A (2003a) Nondominant hand performance of the Japanese Trail Making Test and its mirror version. Arch Phys Med Rehabil 84:691-693.
Toyokura M, Ishida A, Watanabe F, Okada N, Yamazaki M (2003b) Intermanual difference in the Japanese Trail Making Test and its mirror version: intra-subject comparison of the task-completion time, cognitive time, and motor time. Disabil Rehabil 25:1339-1343.
Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 108:1-16.
Weintraub S, Mesulam MM (1989) Neglect: hemispheric specialization, behavioral components and anatomical correlates. In: Handbook of Neuropsychology, Vol 2 (Boller F, Grafman J, eds), pp357-374. Elsevier Science Publishers BV, Amsterdam.
Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D; EXCITE Investigators (2006) Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 296:2095-2104.
Yamada N, Kakuda W, Senoo A, Kondo T, Mitani S, Shimizu M, Abo M (2013) Functional cortical reorganization after low-frequency repetitive transcranial magnetic stimulation plus intensive occupational therapy for upper limb hemiparesis: evaluation by functional magnetic resonance imaging in poststroke patients. Int J Stroke 8:422-429.
Zakzanis KK, Mraz R, Graham SJ (2005) An fMRI study of the Trail Making Test. Neuropsychologia 43:1878-1886.

Copyedited by Li CH, Song LP, Zhao M