Effects of low-frequency repetitive transcranial magnetic stimulation combined with intensive speech therapy on cerebral blood flow in post-stroke aphasia

Takatoshi Hara,MD;Masahiro Abo, MD, PhD; Kentaro Kobayashi,MD; Motoi Watanabe, PhD; Wataru Kakuda, MD, PhD; Atushi Senoo, PhD

Department of Rehabilitation Medicine,The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-Ku, Tokyo 105-8461, Japan

Short title: SPECT study of rTMS and rehabilitation

Key words: single photon emission computed tomography, repetitive transcranial magnetic stimulation, Aphasia, language therapy, functional magnetic resonance imaging

Corresponding author:
Masahiro Abo, MD, PhD,
Department of Rehabilitation, Jikei University School of Medicine,
3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan
Tel: +81-3-3433-1111
Fax: +81-3-5497-4120
E-mail: abo@jikei.ac.jp

Abstract

We provided an intervention to chronic post-stroke aphasic patients using low frequency repetitive transcranial magnetic stimulation (LF-rTMS) guided by a functional magnetic resonance imaging(fMRI) evaluation of language laterality, combined with intensive speech therapy (ST). We performed a single photon emission computed tomography (SPECT) scan pre- and post-intervention, and investigated the relationship between cerebral blood flow (CBF) and language function. Fifty right-handed chronic post-stroke aphasic patients were enrolled in the study. During their 11-day hospital admission, the patients received a 40-min session of 1-Hz LF-rTMS on the left or right hemisphere, according to language localization identified by the fMRI evaluation, and intensive ST daily for 10 days, except for Sunday. A SPECT scan and language evaluation by the Standard Language Test of Aphasia (SLTA) were performed at the time of admission and at 3 months following discharge. We calculated laterality indices (LIs) of regional CBF (rCBF) in 13 language-related Brodmann Area (BA) regions of interest. In patients who received LF-rTMS to the intact right hemisphere (RH-LF-rTMS), the improvement in the total SLTA score was significantly correlated with the pre- and post-intervention change of LI (φLI) in BA44. In patients who received LF-rTMS to the lesional left hemisphere (LH-LF-rTMS), this association was not observed. Analyses of the SLTA subscales and rCBF φLI demonstrated that in the RH-LF-rTMS group, the SLTA Speaking subscale scores were significantly correlated with φLIs in BA11, 20, and 21, and the SLTA Writing subscale scores were significantly correlated with φLIs in BA6 and 39. Conversely, in the LH-LF-rTMS group, the SLTA Speaking subscale scores were correlated with φLI in BA10, and the SLTA Reading subscale scores were significantly correlated with φLIs in BA13, 20, 22, and 44. Our results suggest the possibility that fMRI-guided LF-rTMS combined with intensive ST may affect CBF and contribute to the improvement of language function of post-stroke aphasic patients. LF-rTMS to the non-lesional and lesional hemispheres showed a difference in the associations between language performance and CBF.

The results indicate that more effective rTMS intervention needs to be explored for patients who show right hemisphere language activation in an fMRI language evaluation.

Introduction

Recent studies reported that repetitive transcranial magnetic stimulation (rTMS) improved language function in chronic post-stroke patients with aphasia who sustained an insult to the left hemisphere[1,2]. These studies postulated that the recovery of language function was due to perilesional compensation in the ipsilateral hemisphere, facilitated by reduced interhemispheric inhibition that resulted from inhibitory low-frequency rTMS (LF-rTMS). However, it is also considered that the contralateral homotopic areas contribute as compensatory regions to the recovery of language function in post-stroke aphasia[3-5]. Furthermore, in a study using a functional magnetic resonance imaging (fMRI) language task, patients with aphasia demonstrated stronger activation in the right hemisphere relative to healthy control participants[6]. Therefore, it may be that LF-rTMS to the right hemisphere results in a deterioration of language function in a patient with aphasia whose right hemisphere has already assumeds an important role in language recovery[7]. On the basis of these studies, we proposed a treatment intervention consisting of fMRI-guided selective LF-rTMS combined with intensive speech therapy (ST). This proposed method utilizes fMRI to identify the language regions of each patient and administers LF-rTMS and intensive ST, to achieve the recovery of activity in these identified regions, based on the principles of interhemispheric inhibition. Our previous study conducted under the same premise found a significant improvement in language function in response to LF-rTMS administered to chronic post-stroke patients with aphasia [8]. In addition, previously carried out LF-rTMS Wernickeõs area in fluent aphasia patients and an improvement in the Token Test and subscale scores of the Standard Language Test of Aphasia (SLTA)[9].

In recent years, the effects of rTMS on cerebral networks in chronic post-stroke patients with aphasia have been reported[1,10,11]. However, the effects of fMRI-guided selective LF-rTMS combined with intensive ST on language networks of the brain have not been examined fully.

Single photon emission computed tomography (SPECT) is an application of scintigraphy that detects gamma rays from a radioisotope delivered into a patient, creating a cross-sectional image of the gamma ray distribution. SPECT imaging of the brain is used widely in the clinical setting as a method to obtain physiological and functional information of the brain. Particularly, in recent years, SPECT imaging has been used widely to evaluate and assess treatment effectiveness in the field of rehabilitation[12-14].

In this study, we hypothesized that LF-rTMS to the hemisphere contralateral to the language compensation regions identified by fMRI would result in the recovery of language function. We performed language function evaluation and SPECT imaging in chronic post-stroke patients with aphasia, pre- and post-intervention, consisting of LF-rTMS and intensive ST.

The purpose of the current study was to investigate the different effects that LF-rTMS may have on cerebral blood flow within the hemispheres with and without a stroke lesion. Furthermore, we investigated the relationship between fMRI activation within the language compensatory regions and improvement in language function resulting from selective LF-rTMS and intensive ST.

Subjects and Methods

Patients and Study Protocol

Among the patients with chronic post-stroke aphasia who were admitted to the Tokyo Jikei University Hospital between May 2010 and January 2013, 50 right-handed patients who underwent SPECT scans at the time of admission and at 3 months following discharge were included retrospectively in the current study. None of the patients demonstrated significant language improvement despite receiving outpatient ST for 1ï 3 months. The clinical backgrounds of these patients are summarized in Table 1. The average age at the time of the intervention was 60.3 years with a standard deviation (SD) of 12.1, ranging from 35 to 82 years. Forty patients were men and 10 were women. The stroke subtypes consisted of ischemic in 29 patients, hemorrhagic in 20 patients, and subarachnoid hemorrhage in 1 patient. On the basis of the results of the SLTA described in detail below, the patients were categorized into nonfluent or fluent aphasia [15]. Twenty-seven patients had nonfluent aphasia, while 23 patients had fluent aphasia. The average duration from the onset of stroke to the intervention was 55.9 months. Twenty-nine patients received LF-rTMS to the right non-lesional hemisphere after the fMRI task identified the left hemisphere as the language compensatory hemisphere (RH-LF-rTMS group). Twenty-one patients received LF-rTMS on the lesional left hemisphere after the fMRI evaluation identified the right hemisphere as the language compensatory hemisphere (LH-LF-rTMS group).

The average age of the RH-LF-rTMS group at the time of the intervention was 59.9 years and the group consisted of 22 men and 7 women. Seventeen of these patients had ischemic stroke and 12 had hemorrhagic stroke. Seventeen of these patients had nonfluent aphasia, while 12 had fluent aphasia. The average duration from the onset of stroke to the intervention was 56.2 months.

The average age of the LH-LF-rTMS group at the time of the intervention was 60.9 years and the group consisted of 18 men and 3 women. Twelve of these patients had ischemic stroke, 8 had hemorrhagic stroke, and 1 had subarachnoid hemorrhage. Ten of these patients had nonfluent aphasia, while 11 had fluent aphasia. The average duration from the onset of stroke to the intervention was 55.6 months.

Patients were excluded if they had alteration of consciousness, neurophysiological signs, neurological symptoms that are considered contraindications to LF-rTMS based on Wassermanõs guidelines[16], or evidence of electroencephalographic epileptiform discharges during the duration of the study.

Each patient was admitted to the rehabilitation department for 11 days after receiving an outpatient fMRI language evaluation at 1 week prior to admission. The patients received a total of 10 sessions of 40-min 1-Hz LF-rTMS and 60-min intensive ST (i.e., 1 session per day, except for Sunday). During admission, medical and neurological evaluations were conducted before and after each session to monitor adverse effects and worsening of language function. Prior to participation, the attending physician provided a comprehensive explanation of the planned treatment intervention, and written informed consent was obtained from all patients. Furthermore, the current study was conducted following the approval of the Tokyo Jikei University Institutional Review Board.

Functional Magnetic Resonance Imaging

All MRI was performed on a 3T scanner. The fMRI scan was performed using a gradient echo echo-planar sequence (slice thickness = 5 mm, field of view = 240 mm, TR = 5000 ms, TE = 90.5 ms, flip angle = 80°, and matrix = 128 × 128) at 1 week prior to admission. One fMRI run consisted of 12 cycles of 60-s long ñrepetitionò and ñrestò periods, and the patient completed 4 runs. During the repetition period, the patient overtly repeated back the words that were played every 5 s through earphones, and the patientõs responses were recorded. If the patient correctly repeated greater than half of the words that were presented, the fMRI data were considered valid. If the patient repeated fewer than half of the words, the fMRI session was repeated. The horizontal and coronal views of a standard T1-weighted image (slice thickness = 2 mm, field of view = 240 mm, TR = 26 ms, TE = 2.4 ms, and matrix = 256 168 × 256) were used to register the fMRI image to the structural data in order to localize accurately the activation regions. The fMRI data were analyzed with SPM2 (Wellcome Department of Cognitive Neurology) implemented in MATLAB (MathWorks, Natick, MA, USA), and an alpha of 0.01 was used as a significance threshold for brain activation.

Evaluation of Language Function

Language function was evaluated by the SLTA[15]. The SLTA is a widely used standardized language test to evaluate the language function of native speakers of the Japanese language. This instrument evaluates various language functions including speaking, reading, naming, repetition, listening, discourse, discourse comprehension, writing, and calculation. In the current study, we evaluated the patientsôlanguage function using 4 of the subscales, i.e., Speaking, Listening, Reading, and Writing. A total SLTA score below 100 was categorized as severely impaired, 100 - 140 as moderately impaired, and above 140 as mildly impaired. The SLTA was performed at the time of admission and at 3 months following discharge.

Therapeutic Application of Low-Frequency rTMS

LF-rTMS (MagVenture Company, Farum, Denmark) was administered to the patient in a sitting position, using an 8-shaped 70-mm coil and a MagPro R30 stimulator. During admission, each patient received 1 LF-rTMS session every day, except for Sunday, which came to a total of 10 sessions. One session of 1-Hz LF-rTMS lasted for 40 min (2400 total stimulations). Stimulation intensity was at 90% of each individual patientôs motor threshold intensity, with motor threshold intensity defined as the smallest stimulation intensity in the left first dorsal interosseous muscle that could induce a motor evoked potential.

In a previous study, this threshold has been shown to be safe according to Wasserman's guidelines[16]. Prior to each session, this motor threshold intensity was measured by stimulating the primary motor cortex within the right hemisphere. LF-rTMS was performed by the attending physicians, and in the case of adverse events or side effects, the treatment was terminated immediately.

The LF-rTMS stimulation site was determined based on the fMRI results and the type of aphasia, as described previously[8]. Using the fMRI task, we determined the hemisphere that was responsible for compensation of language function, as well as the region that was the most active. Under the aforementioned fMRI scanning conditions, no case exhibited activation of the bilateral cerebral hemispheres, but the activation sites were identified unilaterally on the right or left. Similarly, no case showed multiple active areas.

The aphasia types were categorized using the SLTA prior to the intervention. LF-rTMS was administered to the inferior frontal gyrus (IFG) and superior temporal gyrus (STG) for patients with nonfluent and fluent aphasia, respectively. Jennum et al. defined the language areas by the international 10-20 electrode system[17] to apply inhibitory LF-rTMS[18]. In the international 10-20 electrode system, F7/8 and CP5/6 correspond to the IFG and STG, respectively. Therefore, we chose F7/8 as the stimulation target site for the patients with non-fluent aphasia, and CP5/6 for those with fluent aphasia. We adopted the stimulation threshold for them because its efficacy has been proven in previous studies [2,9,26].

In the aphasia patients who sustained an insult to the left cerebral cortex due to stroke, the compensatory language region may change over time during the recovery process. Therefore, it is essential to identify accurately the compensatory language regions prior to delivering therapeutic rTMS. We used language task fMRI in order to identify the compensatory language regions that developed in response to the loss of previous language function. We hypothesized that LF-rTMS to the hemisphere contralateral to the identified compensatory language regions combined with concurrent intensive ST should reduce interhemispheric inhibition and facilitate neuronal activity in the compensatory regions, which may result in improved language function. We used LF-rTMS because it has a much lower risk of inducing seizures relative to high-frequency rTMS, and its effects may extend broadly including the hemisphere contralateral to the stimulation site.

Intensive Speech Therapy

A speech therapist provided a one-on-one intensive ST session for 60 min in an individual room. The purpose of this ST was to improve the patientõs expressive modalities including language expression, repetition, naming, and writing. All communication was limited to verbal communication, and communication through gestures and drawing was prohibited.

The therapy consisted of 3 main tasks. First, the patient was asked to describe and answer questions about a photograph or a short comic depicting a typical object or situation from everyday life. In addition, the patient was asked to recall the names of objects and scenes presented previously in the photographs and comics. Second, the patient was asked to repeat words and short sentences multiple times that were presented by the therapist. Third, the patient was asked to dictate words and sentences presented by the therapist. During the training, the speech therapist encouraged the patient to make an attempt to work on their communication skills as much as possible. The difficulty level of the training was increased gradually based on the levels of observed improvement of language function during the intensive ST training. During the 3 months following discharge, the patients continued outpatient ST. The skills attained during the intensive ST and their related skills were trained further during this follow-up period. Feedback for attained communication skills was given to the patient on a regular basis in order to reinforce the obtained skills.

Single Photon Emission Computed Tomography and Laterality Index

We used SPECT to measure the regional cerebral blood flow (rCBF) of each patient. SPECT studies were performed at the time of admission and at 3 months following discharge with 99mTc-ethyl cysteine dimer (99mTc-ECD) as a tracer. We used a gamma camera with a low-energy high-resolution collimator (MultiSPECT3; Siemens PANA K.K., Tokyo, Japan). SPECT acquisition was performed at 20 min after an intravenous injection of 600 MBq 99mTc-ECD while the patient was resting in a supine position with their eyes closed. Attenuation correction of the SPECT images was achieved by Changĝs method[19]. SPECT acquisition was performed with the following parameters: step-and-shoot acquisition, fan beam collimator, matrix size = 128 × 128, 138 KeV window, 30 s/direction scan time, voxel size = 2.46 mm, Butterworth pre-processing filter (5th order, cutoff frequency 0.3 cycles/cm), and ramp reconstruction filter. Image analyses were carried out by the first author of the current study.

Statistical Analysis

The SPECT images were standardized anatomically and smoothed using SPM5. The count was normalized to the whole brain count, and volume of interest values of the selected regions were calculated[20,21]. Thirteen language-related Brodmann area (BA) regions (BA8, 9, 10, 13, 20, 21, 22, 39, 40, 44, 45, and 46) were selected prior to the analyses. For each of the BA regions, a laterality index (LI; ranging from -1 to +1) was calculated as follows: LI = (lesion side rCBF ï non-lesion side rCBF) / (lesion side rCBF + non-lesion side rCBF).

Next, using these LIs, the LI change ratio from before to after the intervention (ΔLI) was calculated. For the denominator, the absolute value of the pre-intervention LI was used. By doing so, a positive ΔLI would indicate a change toward the lesion hemisphere, while a negative ΔLI would indicate a laterality change toward the non-lesion hemisphere. For the SLTA total scores and SLTA subscale scores, paired t-tests were performed. In order to investigate associations between the SLTA scores and ΔLIs, Spearmanôs rank correlation coefficients were calculated. These correlation analyses were performed selectively on the 13 BA regions associated with aphasia, instead of all BA regions. Therefore, corrections for multiple comparison were not carried out, and an alpha of 0.05 was used21. All statistical analyses were performed with IBM SPSS Statistics 22.

Results

All 50 patients completed the 11-day treatment protocol, and no adverse events were noted during admission. In addition, no adverse events were reported during the 3 months following discharge.

Table 2 shows the change of the total SLTA scores over time. The SLTA total mean score improved from 148.8 to 154.7 and 127.0 to 133.6 in the RH-LF-rTMS and LH-LF-rTMS groups, respectively (p < 0.01). When the SLTA subscales were compared, the RH-LF-rTMS group demonstrated a significant improvement in the Speaking (from 59.4 to 61.1), Reading (from 34.2 to 34.9), and Writing (25.0 to 26.4) subscales. The LH-LF-rTMS group demonstrated a significant improvement in the Listening (28.4 to 30.0), Speaking (46.2 to 49.0), and Writing (21.0 to 22.6) subscales.

Correlation analyses between the SLTA total change scores and rCBF ΔLIs showed that a statistically significant association was found in BA44 in the RH-LF-rTMS group (r = 0.402, p < 0.05, R2 = 0.144, Figure 1). However, the LH-LF-rTMS group did not show any significant association between the SLTA total change scores and rCBF ΔLIs.

When the SLTA subscale change scores and rCBF ΔLIs were examined in the RH-LF-rTMS group, statistically significant associations were detected in BA11, 20, and 21 for the Speaking subscale (r = 0.456, p < 0.05, R2 = 0.184; r = 0.437, p < 0.05, R2 = 0.112; and r = 0.376, p < 0.05, R2 = 0.089, respectively), and in BA6 and 39 for the Writing subscale (r = 0.574, p < 0.01, R2 = 0.311; and r = 0.384, p < 0.05, R2 = 0.157, respectively). In the LH-LF-rTMS group, significant associations were found in BA10 for the Speaking subscale (r = -0.683, p < 0.01, R2 = 0.353) and in BA13, 20, 22, and 24 for the Reading subscale (r = 291 -0.460, p < 0.05, R2 = 0.338; r = -0.530, p < 0.05, R2 = 0.286; r = -0.552, p < 0.01, R2 = 0.264; and r = -0.461, p < 0.05, R2 = 0.285, respectively). Tables 3 and 4 show the correlation coefficients between the SLTA scores and rCBF ΔLIs.

Discussion

Recently, there has been accumulating evidence of the effectiveness of LF-rTMS in patients with post-stroke aphasia[1,2,21,23-26]. LF-rTMS is often applied to the contralesional homotopic regions based on the principles of reduces interhemispheric inhibition and facilitation of neuronal activity in the compensation regions[25]. Naeser et al. reported that LF-rTMS to the right hemisphere in patients with post-stroke aphasia led to an improvement of language function[23,24]. On the basis of their results, the authors speculated that LF-rTMS reduced the interhemispheric inhibition arising from the lesional hemisphere. In addition, Thiel et al. investigated the pre- and post-intervention changes of language activation in response to LF-rTMS to the right pars triangularis in subacute post-stroke patients with aphasia using O-15-water positron emission tomography (PET). The authors demonstrated a significant correlation between the improvement in language performance and changes measured in the PET images. Furthermore, this study also visualized patientsôPET activation regions in comparison to those of healthy controls[1].

Conversely, other research groups proposed that right hemisphere activity is necessary to compensate for the lost language function observed in chronic post-stroke patients with aphasia[8,27-29]. For instance, in a review of imaging studies of subacute and chronic post-stroke patients with aphasia, Price et al. discussed one study showing right hemisphere activation was correlated with improved language performance, raising the possibility of a contribution of right hemisphere activation to language recovery in chronic aphasia patients[30]. Richter et al. reported that greater right hemisphere activation was observed in patients with aphasia than in controls in response to language task fMRI, showing that language performance recovery was associated with a relative reduction in right hemisphere activation, and that changes within the left hemisphere did not correlate with language recovery[6]. Therefore, these data support a view that right hemispheric activation in chronic post-stroke patients with aphasia may not always be a maladaptive reaction, as proposed by Naeserôs group. In particular, Hamilton et al. pointed out that the degree to which the right hemisphere network contributes to language recovery in post-stroke aphasia may depend on the time course of the injury[3]. In addition, Heiss and Thiel discussed that the size and location of a lesion within the left hemisphere may determine how the right hemisphere would contribute to language recovery[3,4]. Heiss and Thiel also suggested that in the case of an insult affecting a broad ipsilateral region, language recovery would have to depend on a very small remaining area in the left hemisphere or on homotopic right hemisphere regions. In such cases, the effects of LF-rTMS to the right hemisphere may remain small. Given these past studies, we utilized an fMRI repetition task to identify the language activation regions in order to guide LF-rTMS intervention[8].

Thielȏs group calculated LIs of PET activation within both hemispheres in investigations of LF-rTMS in post-stroke patients with aphasia[1,26]. These studies examined the relationship between pre- and post-intervention LI changes and language recovery. Similarly, we examined pre- and post-intervention changes using SPECT after identifying language-related regions of interest (ROIs), and investigated the change ratios of LIs in each ROI and language performance

changes. We believed that this approach would enable us to study the effects of right hemispheric LF-rTMS on the left hemisphere and the effects of left hemispheric LF-rTMS on the right.

A SPECT study examining the effects of rTMS on CBF reported a correlation between LI changes in motor regions and upper limb motor function following LF-rTMS to the non-lesional hemisphere of post-stroke patients with upper limb hemiparesis12. We used LIs due to their wide use in investigating changes in neural plasticity and neuromodulation due to LF-rTMS. As the lesions in these patients were extensive and variable, we judged that it was not ideal to subject their whole brain images to group statistical analyses. Therefore, we measured the changes in rCBF LIs by measuring the accumulation of radioisotopes in the language-related regions.

Although the number of patients differed between our RH-LF-rTMS and LH-LF-rTMS groups, there was no statistically significant difference between both groups with respect to age and the duration from the onset of aphasia to intervention. However, in terms of the severity of aphasia as measured by the SLTA total scores, a greater proportion of patients were classified as severely impaired in the LH-LF-rTMS group. This may indicate that the insult to the lesional (left) hemisphere was severe, and the reduction of activity in the language areas in the left hemisphere elicited compensatory activity in the non-lesional (right) hemisphere, and that there was no shift of the compensatory regions from the non-lesional (right) hemisphere to the lesional (left) hemisphere[3,31].In the current study, we performed LF-rTMS after identifying the language activation areas and observed a significant improvement in language function. Similar to previous PET studies, pre- and post-rTMS LI changes were associated with an improvement in language performance, and the results suggested that right hemisphere LF-rTMS may contribute to language function. It is of note that both the SLTA total and SLTA subscale scores showed associations with LI changes in the language regions in this group. Conversely, in the LH-LF-rTMS group, a significant correlation between LI changes and language performance improvement was limited to the SLTA subscales .

This improvement in language function is in line with our previous study demonstrating the effectiveness of LF-rTMS based on the principle of interhemispheric inhibition. In addition, our results suggest that the effects of neuromodulation on language regions via an interhemispheric network may be different between the RH-LF-rTMS and LH-LF-rTMS groups.

In the RH-LF-rTMS group, there was an association between the total SLTA score and rCBF φLI in BA44 .

Left BA44 is part of the dorsal pathway of language that is involved in acoustic speech and is considered to be responsible for articulatory and syntactic processes[32,33]. A previous PET study on chronic post-stroke aphasia patients found that an increase in rCBF in the left BA44 during a repetition task correlated with Western Aphasia Battery scores of spontaneous speech[27]. Furthermore, a series of studies on language recovery in post-stroke aphasic patients conducted by Naeserφs group suggested that LF-rTMS to the right pars triangularis was effective, and that the pars opercularis was essential in language recovery[1,23,24]. The results of the current study are in line with these previous studies. With regard to the association between the rCBF φLIs of BA11, 20, and 21 and the SLTA Speaking subscale scores, BA11 is connected anatomically via the uncinate fasciculus to the anterior temporal lobe, which is part of the semantic memory network and is involved in lexical retrieval[34,35]. BA20 is involved in phonological and semantic processing, and BA21 is part of the ventral pathway of language that is responsible for semantic processing and sentence comprehension[32,33]. In a longitudinal PET study investigating language function in chronic post-stroke aphasia patients during the subacute phase and at 1 year later, left BA20 showed a correlation with improved language performance[36]. Therefore, these regions are considered to play an essential role in the abilities measured by the SLTA Speaking subscale. With regard to the association between the rCBF φLIs and BA6 and 39 and the SLTA Writing subscale scores, BA6 is generally involved in smooth motor programming and motor planning processes, and is a constituent of verbal working memory in language function[27,37]. In addition, Martin et al. reported fMRI activation in the supplementary motor area (SMA) at the 16th month follow-up of LF-rTMS to the right pars triangularis in chronic post-stroke aphasia patients[38]. This observation suggests a possibility of neuromodulation within the left SMA during long-term follow-up of rTMS. BA39 is believed to be involved in the auditory short-term memory process that is associated with the ñphonological loop,ò which consists of a phonological store that is an auditory-motor interface, and the articulatory rehearsal system[39]. Therefore, the results indicate the possibility that rTMS and intensive rehabilitation resulted in the activation of the left hemisphere regions responsible for executing writing movements by incorporating relevant auditory information, which is an ability associated with what is measured by the SLTA Writing subscale.

Conversely, the changes in each of the ROIs and SLTA scores of the LH-LF-rTMS group support the view that our treatment intervention based on the principle of interhemispheric inhibition resulted in the transition of LIs from the originally dominant left hemisphere to the right hemisphere, and this transition was associated with an improvement in language performance. The regions in the right hemisphere that correlated with the SLTA Speaking and Reading subscales are homotopic to the left regions that are responsible for their respective language functions[1,33,40]. Temporary activation of the homotopic language areas during language recovery and ST has been reported in BA13 and 22[41,42]. However, the effects of rTMS on these language-related homotopic regions have not been examined fully.

In the current study, there was a difference between the RH-LF-rTMS and LH-LF-rTMS groups. With respect to the patientsôclinical background, the LH-LF-rTMS group showed lower mean SLTA scores and greater severity of aphasia relative to the RH-LF-rTMS group. Saur et al. discussed three temporary phases of language recovery that may explain this discrepancy. The authors postulated that patients with an extensive lesion within the left language area may remain at the second phase where the right hemisphere compensates for the lost abilities and may not proceed to the third phase where reactivation of the lesional hemisphere occurs[5]. An extensive lesion within the left hemisphere would limit compensation by the perilesional areas, and it is possible that activation in the perilesional areas does not occur in response to the fMRI repetition task[3]. There are two hypotheses regarding the mechanism of the effects of LH-LF-rTMS. The first is that LF-rTMS strengthens right hemisphere compensatory activation through interhemispheric networks. The second is the possibility that LF-rTMS to the left hemisphere prohibits the activation of perilesional regions that would have occurred otherwise. Differential mechanisms of left and right hemisphere LF-rTMS are suggested, and future investigations are warranted.

We chose the rTMS stimulation sites based on the past literature, but the regions where CBF LI changes and language performance improvements were observed were broader than the regions to which rTMS was applied. LF-rTMS to chronic post-stroke patients with upper limb paralysis reportedly not only modulated neural connectivity within the hemisphere to which rTMS was applied but also affected distant brain regions9. In addition, it is suggested that the effects observed following rTMS are not so much due to excitation of individual motor regions than they are due to the remodeling of cerebral networks10.

It is plausible that similar effects of rTMS on cerebral networks are observed in post-stroke aphasic patients, but future studies are needed to investigate this.

The first limitation of the current study is that it was not a randomized controlled trial. Ideally, the current protocol should be compared with conventional ST intervention. However, based on the number of cases, we judged that it would be difficult to conduct 2 sessions of SPECT imaging on patients who were receiving conventional ST; therefore, we did not include them as a comparison. Second, we did not observe an association between the SLTA total improvement and rCBF LI changes in the LH-LF-rTMS group.

Recently, one study reported utilizing dual-hemisphere rTMS for subacute post-stroke aphasia43. Khedr et al. discussed that the effects of dual-hemisphere rTMS on patients with complete middle cerebral artery occlusion were not sufficient and that high-frequency rTMS to the right hemisphere may be necessary.

Thirdly, we carried out no fMRI after the intervention. Since Thiel et al. had proven the utility of magnetic stimulation therapy for aphasia by PET, we first tried verification by SPECT1,26. We are planning to measure the change in activation before and after the intervention by fMRI.

Future studies are needed to investigate whether rTMS should aim to increase the activation of the right hemisphere or to shift language activation to the left hemisphere for those patients whose unaffected (right) hemisphere has significant activation.

The method that we used, has not been studied sufficiently. In particular, the number of chronic post-stroke aphasia cases to whom LF-rTMS was applied to the left hemisphere was small and additional studies are warranted.

In summary, Our results suggest the possibility that fMRI-guided LF-rTMS combined with intensive ST may affect CBF and contribute to the improvement of language function in post-stroke aphasic patients. LF-rTMS to the non-lesional and lesional hemispheres showed a difference in the associations between language performance and CBF. The results indicate that more effective rTMS intervention needs to be explored for patients who show right hemisphere language activation in an fMRI language evaluation.

Acknowledgments

The authors gratefully acknowledge the participation of the patients in the study. This work was supported by the Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

Conflict of Interest

Takatoshi Hara, Masahiro Abo, MD, Kentaro Kobayashi, Motoi Watanabe, Wataru Kakuda and Atushi Senoo declare that they have no conflict of interest.

Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

References

1. Thiel A, Hartmann A, Rubi-Fessen I, et al. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. Stroke 2013;44:2240-6. doi: 10.1161/STROKEAHA.111.000574. Epub 2013 Jun 27.

2. Naeser MA, Martin PI, Theoret H, et al. TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. Brain Lang 2011;119:206-13. doi: 10.1016/j.bandl.2011.07.005. Epub 2011 Aug 23.

3. Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 2011;118:40-50. doi: 10.1016/j.bandl.2011.02.005. Epub 2011 Apr 2.

4. Heiss WD, Thiel A. A proposed regional hierarchy in recovery of post-stroke aphasia. Brain Lang 2006;98:118-23.

5. Saur D, Lange R, Baumgaertner A, et al. Dynamics of language reorganization after stroke. Brain 2006;129:1371-84.

6. Richter M, Miltner WH, Straube T. Association between therapy outcome and right-hemispheric activation in chronic aphasia. Brain 2008;131:1391-401.

7. Finger S, Buckner RL, Buckingham H. Does the right hemisphere take over after damage to Broca's area? the Barlow case of 1877 and its history. Brain Lang 2003;85:385-95.

8. Abo M, Kakuda W, Watanabe M, Morooka A, Kawakami K, Senoo A. Effectiveness of low-frequency rTMS and intensive speech therapy in poststroke patients with aphasia: a pilot study based on evaluation by fMRI in relation to type of aphasia. Eur Neurol 2012;68:199-208. doi: 10.1159/000338773. Epub 2012 Aug 29.

9 Kakuda W, Abo M, Uruma G, Kaito N, Watanabe M. Low-frequency rTMS with language therapy over a 3-month period for sensory-dominant aphasia: case series of two post-stroke Japanese patients. Brain injury . 2010 ; 24 :1113-7.

10. Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 2010;50:233-42. doi: 10.1016/j.neuroimage.2009.12.029. Epub 2009 Dec 18.

11. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain 2011;134:1264-76. doi: 10.1093/brain/awr033. Epub 2011 Mar 16.

12. Hara T, Kakuda W, Kobayashi K, Momosaki R, Niimi M, Abo M. 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. The Jpn J Rehabil Med 2013;50:36-42.

13. Takekawa T, Kakuda W, Uchiyama M, Ikegaya M, Abo M. Brain perfusion and upper limb motor function: a pilot study on the correlation between evolution of asymmetry in cerebral blood flow and improvement in Fugl-Meyer Assessment score after rTMS in chronic post-stroke patients. J Neuroradiol 2014;41:177-83. doi: 10.1016/j.neurad.2013.06.006. Epub 2013 Jul 22.

14. Kononen M, Kuikka JT, Husso-Saastamoinen M, et al. Increased perfusion in motor areas after constraint-induced movement therapy in chronic stroke: a single-photon emission computerized tomography study. J Cereb Blood Flow Metabo 2005;25:1668-74.

15. Hasegawa T, Kishi H, Shigeno K. A Study on Aphasia Rating Scale. A Method for Overall Assessment of SLTA Results. Higher Brain Function Research 1984;4:638-46.

16. Wassermann EM. 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 1998;108:1-16.

17. Homan RW, Herman J, Purdy P. Cerebral location of international 10-20 system electrode placement. Electroencephalogr Clin Neurophysiol 1987;66:376-82.

18. Jennum P, Friberg L, Fuglsang-Frederiksen A, Dam M. Speech localization using repetitive transcranial magnetic stimulation. Neurology 1994;44:269-73.

19. Ohnishi T, Matsuda H, Hashimoto T, et al. Abnormal regional cerebral blood flow in childhood autism. Brain 2000;123 (Pt 9):1838-44.

20. Friston K, Holmes A, Worsley K, Poline JB, Frith C, Frackowiak R. Statistical

parametric maps in functional imaging : a general linear approach. Human brain mapping 1995;2:189-210.

21. Ashburner J, Friston KJ. Nonlinear spatial normalization using basis functions.Hum Brain Mapp 1999;7:254-66.

22. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007;18:805-35.

23. Naeser MA, Martin PI, Nicholas M, et al. Improved naming after TMS treatments in a chronic, global aphasia patient--case report. Neurocase 2005;11:182-93.

24. Naeser MA, Martin PI, Nicholas M, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang 2005;93:95-105.

25. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005;36:2681-6.

26. Weiduschat N, Thiel A, Rubi-Fessen I, et al. Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. Stroke 2011;42:409-15. doi: 10.1161/STROKEAHA.110.597864. Epub 2010 Dec 16.

27. Ohyama M, Senda M, Kitamura S, Ishii K, Mishina M, Terashi A. Role of the nondominant hemisphere and undamaged area during word repetition in poststroke aphasics. A PET activation study. Stroke 1996;27:897-903.

28. Abo M, Senoo A, Watanabe S, et al. Language-related brain function during word epetition in post-stroke aphasics. Neuroreport 2004;15:1891-4.

29. Abo M, Takao H, Hashimoto K, Suzuki M, Kaito N. Re-organization of language function within the right hemisphere. Eur J Neurol 2007;14:e7-8.

30. Price CJ, Crinion J. The latest on functional imaging studies of aphasic stroke. Curr

Opin Neurol 2005;18:429-34.

31. Berthier ML, Garcia-Casares N, Walsh SF, et al Recovery from post-stroke aphasia: lessons from brain imaging and implications for rehabilitation and biological treatments. Discov Med 2011;12:275-89.

32. Saur D, Kreher BW, Schnell S, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A. 2008;105:18035-40. doi: 10.1073/pnas.0805234105. Epub 2008 Nov 12.

33. Vigneau M, Beaucousin V, Herve PY, et al. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing.NeuroImage 2006;30:1414-32.

34. Papagno C. Naming and the role of the uncinate fasciculus in language function. Current neurology and neuroscience reports 2011;11:553-9. doi: 10.1007/s11910-011-0219-6.

35. Duffau H, Gatignol P, Moritz-Gasser S, Mandonnet E. Is the left uncinate fasciculus essential for language? A cerebral stimulation study. Journal of neurology 2009;256:382-9. doi: 10.1007/s00415-009-0053-9. Epub 2009 Mar 6.

36. de Boissezon X, Demonet JF, Puel M, et al. Subcortical aphasia: a longitudinal PET study. Stroke 2005;36:1467-73.

37. Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. Nature 1993;362:342-5.

38. Martin PI, Naeser MA, Ho M, et al. Overt naming fMRI pre- and post-TMS: Two nonfluent aphasia patients, with and without improved naming post-TMS. Brain and language 2009;111:20-35. doi: 10.1016/j.bandl.2009.07.007. Epub 2009 Aug 19. Erratum in: Brain Lang. 2010 Feb;112(2):135. Alonso, Miguel [added].

39. Dronkers NF, Wilkins DP, Van Valin RD, Jr., Redfern BB, Jaeger JJ. Lesion analysis of the brain areas involved in language comprehension. Cognition 2004;92:145-77.

40. Eckert MA, Menon V, Walczak A, et al. At the heart of the ventral attention system:

the right anterior insula. Human brain mapping 2009;30:2530-41. doi: 10.1002/hbm.20688.

41. Raboyeau G, De Boissezon X, Marie N, et al. Right hemisphere activation in recovery from aphasia: lesion effect or function recruitment? Neurology 2008;70:290-8. doi: 10.1212/01.wnl.0000287115.85956.87.

42. Specht K, Zahn R, Willmes K, et al. Joint independent component analysis of structural and functional images reveals complex patterns of functional reorganisation in stroke aphasia. NeuroImage 2009;47:2057-63. doi: 10.1016/j.neuroimage.2009.06.011. Epub 2009 Jun 11.

43. Khedr EM, Abo El-Fetoh N, Ali AM, et al. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. Neurorehabilitation and neural repair 2014;28:740-50. doi: 10.1177/1545968314521009. Epub 2014 Feb 6.

Figure Legends

Fig. 1. BA44: rCBF ΔLIs vs. SLTA total change in the RH-LF-rTMS group

:In the RH-LF-rTMS group, the increase in SLTA total change scores was positively correlated with a increase in rCBF ΔLIs in BA44 ($r = 0.402$, $p < 0.05$, R2 = 0.144). A positive ΔLI indicates a change toward the lesion hemisphere. This suggests that there is relationship between the improvement in language function and rCBF ΔLIs toward the lesion hemisphere. The straight line indicates regression. The curved lines indicate the 95% confidence limit.

Table 1. Subjects' Data

		All patients (n = 50)	Contralesional (Rt) stimulation (n = 29)	Ipsilesional (Lt) stimulation (n = 21)	P value
Age at treatment (years)		60.3 ± 12.1	59.9 ± 11.1	60.9 ± 13.5	0.687
Male / Female		40/10	22/7	18/3	0.565
Type of stroke	Cerebral infarction	29	17	12	
	Intracerebral hemorrhage	20	12	8	
	Subarachnoid hemorrhage	1	0	1	0.811
Type and severity of aphasia	Nonfluent/fluent	27/23	16/13	11/10	0.847
Severity of aphasia	Mild	24	15 (51.7%)	9 (42.9%)	
	Moderate	16	11 (38%)	5 (23.8%)	
	Severe	10	3 (10.3%)	7 (33.3%)	0.216
Time between onset and treatment (months)		55.9 ± 38.0	56.2 ± 33.0	55.6 ± 43.2	0.458

Table 2. Evaluation of language function

	Contralesional (Rt) stimulation		Ipsilesional (Lt) stimulation	
	before	after	before	after
SLTA total (Max score: 210)	148.8 ± 47.7	154.7 ± 46.6**	127.0 ± 55.2	133.6 ± 55.3**
Listening	31.1 ± 7.9	32.0 ± 6.5	28.4 ± 9.7	30.0 ± 8.0*
Speaking	59.4 ± 23.3	61.1 ± 23.7**	46.2 ± 29.0	49.0 ± 30.5**
Reading	34.2 ± 6.3	34.9 ± 5.9**	31.4 ± 8.4	31.9 ± 8.6
Writing	25.0 ± 12.6	26.4 ± 12.1*	21.0 ± 12.2	22.6 ± 12.7**

Table 3. Contralesional (Rt) stimulation, correlation between changes in ΔLI and SLTA in Brodmann's areas (BAs)

	SLTA total		Auditory comprehension		Spontaneous speech		Reading comprehension		Writing	
	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
BA6	0.361	0.055	0.294	0.122	0.017	0.930	0.205	0.285	**0.574**	**0.001****
BA8	0.202	0.294	0.038	0.844	0.218	0.256	0.022	0.910	0.188	0.328
BA9	-0.185	0.336	-0.155	0.422	0.095	0.626	-0.074	0.703	-0.309	0.102
BA10	-0.176	0.361	-0.270	0.148	-0.004	0.982	-0.214	0.265	0.172	0.373
BA11	0.075	0.699	-0.158	0.414	**0.456**	**0.012***	-0.122	0.530	-0.264	0.167
BA13	0.098	0.614	0.207	0.281	0.008	0.968	-0.220	0.253	0.354	0.060
BA20	0.309	0.102	-0.070	0.717	**0.437**	**0.017***	-0.095	0.625	0.159	0.409
BA21	0.367	0.050	0.225	0.241	**0.376**	**0.044***	0.036	0.852	-0.035	0.858
BA22	0.251	0.189	0.203	0.290	0.184	0.339	-0.133	0.493	0.323	0.087
BA39	0.329	0.081	0.193	0.317	0.106	0.584	0.086	0.658	**0.384**	**0.039***
BA40	0.278	0.144	0.243	0.204	0.210	0.273	0.108	0.576	0.103	0.594
BA44	**0.402**	**0.030***	0.306	0.106	0.102	0.600	0.136	0.480	0.361	0.055
BA45	0.118	0.543	0.149	0.441	-0.022	0.909	0.068	0.728	0.153	0.427
BA46	0.134	0.488	0.214	0.266	0.149	0.440	-0.131	0.497	-0.064	0.742

Table 4. Ipsilesional (Lt) stimulation, correlation between changes in ΔLI and SLTA in Brodmann's areas (BAs)

	SLTA total		Auditory comprehension		Spontaneous speech		Reading comprehension		Writing	
	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
BA6	0.017	0.942	0.304	0.180	-0.259	0.258	-0.208	0.365	-0.130	0.574
BA8	0.094	0.684	-0.072	0.755	0.033	0.258	-0.181	0.431	0.045	0.846
BA9	-0.020	0.930	-0.254	0.266	0.139	0.547	-0.125	0.589	-0.016	0.945
BA10	-0.227	0.322	0.073	0.753	**−0.683**	**0.0006****	-0.048	0.836	0.311	0.171
BA11	-0.009	0.971	0.189	0.411	-0.130	0.574	-0.143	0.537	-0.094	0.684
BA13	-0.022	0.926	0.045	0.845	0.111	0.633	**−0.460**	**0.036***	-0.093	0.689
BA20	-0.338	0.134	0.174	0.452	-0.132	0.570	**−0.530**	**0.013***	-0.400	0.073
BA21	-0.372	0.097	0.030	0.899	-0.125	0.589	-0.039	0.867	-0.385	0.085
BA22	-0.053	0.819	0.100	0.667	0.020	0.930	**−0.552**	**0.0095****	-0.180	0.435
BA39	-0.030	0.899	0.187	0.418	-0.155	0.504	-0.413	0.063	-0.021	0.927
BA40	0.252	0.271	-0.006	0.980	-0.166	0.471	0.127	0.585	0.297	0.192
BA44	-0.220	0.338	0.176	0.445	-0.177	0.443	**−0.461**	**0.035***	-0.286	0.209
BA45	-0.211	0.358	0.048	0.836	-0.183	0.426	-0.336	0.136	-0.156	0.500
BA46	-0.094	0.684	0.060	0.797	0.152	0.511	-0.350	0.120	-0.023	0.920

Figure 1. BA 44 : rCBF φL.I. vs. SLTA total change in the RH-LF-rTMS group