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HIGHLIGHTS

- Repetitive transcranial magnetic stimulation has positive effect.
- The involvement of Broca's area did not significantly affect improvement of post-stroke aphasia.

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Conflict of Interest
The corresponding author of this manuscript is an editor of *Brain & NeuroRehabilitation*.

ABSTRACT

This study investigated the differences in the effect of repetitive transcranial magnetic stimulation (rTMS) between patients with and without the involvement of Broca's area (IBA). The medical records of 20 stroke patients treated with rTMS for non-fluent aphasia were reviewed. Patients completed the Korean version of the Western Aphasia Battery (K-WAB) pre- and post-rTMS. Magnetic resonance T1-weighted images of the brain were analyzed using SPM12 software. Montreal Neurological Institute templates and Talairach coordinates were used to determine Broca's area involvement and segregate patients into 2 groups: IBA and non-IBA (NBA) groups. All statistical analyses were performed using the SPSS software. Twenty subjects were included in the study. The K-WAB scores revealed improvements in the total subjects and IBA and NBA groups. There were no statistical differences between the IBA and NBA groups in the ΔK-WAB scores of aphasia quotient, fluency, comprehension, repetition, and naming. The rTMS was positive for non-fluent aphasia patients, but there was no significant difference in effectiveness depending on the IBA. Further research with a larger number of patients is needed to identify the differences in the effect of rTMS on the IBA.

Keywords: Aphasia; Broca's Area; Language Tests; Stroke; Transcranial Magnetic Stimulation

INTRODUCTION

According to 2018 domestic statistics, stroke is the fourth leading cause of death in Korea, after cancer, heart disease, and pneumonia [1]. The recovery of functions is not complete after stroke, and most patients suffer from disabilities [2]. Aphasia, which is common after stroke, is associated with mortality, disability, and the use of health services [3].

Treatment for post-stroke aphasia includes speech and language therapy (SLT), medication therapy, and repetitive transcranial magnetic stimulation (rTMS). SLT improves functional communication, reading, writing, and expressive language. It is more effective at high intensities and doses [4]. Medications, such as cholinesterase inhibitors, used in

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combination with SLT, have a positive effect on spontaneous speech, comprehension, and naming through compensation for damage to the neurotransmitter pathway [5].

Recently, rTMS has been used as a part of a neurorehabilitation strategy in post-stroke treatment. Transcranial magnetic stimulation can produce an electric field in the brain cortex by generating a magnetic pulse and subsequently modulating gamma-aminobutyric acid inhibition. Stimulating the brain cortex via rTMS can correct maladaptive neuroplasticity after stroke or improve adaptive neuroplasticity during rehabilitation [6]. This aims to enhance recovery from functional impairment after stroke by locally modifying cortical excitability or altering neural network connections. The rTMS has been applied to various functional impairments such as motor weakness, aphasia, dysphagia, and neglect after stroke, and evidence for its therapeutic effect is accumulating [7]. In particular, there is positive evidence regarding the application of rTMS in motor recovery [8,9]. However, the evidence is weak regarding the effectiveness of rTMS in patients with aphasia. A meta-analysis of small randomized controlled trials has reported that low-frequency rTMS (LF rTMS) targeting the pars triangularis of the right inferior frontal gyrus (the right homologue to Broca's area), may have a positive effect on aphasia in stroke patients [10]. LF rTMS to the right homologue of Broca's area downregulates the increased cortical activity of the opposite hemisphere and improves post-stroke non-fluent aphasia [11,12].

Several factors such as age, aphasia type, severity of aphasia, and lesion-related factors influence recovery from post-stroke aphasia [13]. Some studies have reported that lesions in the superior temporal gyrus are associated with poor aphasia recovery globally or Wernicke's aphasia [14,15]. In a recent study using brain magnetic resonance (MR) mapping images, Broca's area and superior temporal gyrus were associated with a poor prognosis of recovery from aphasia after stroke [16]. The study indicates that the involvement of Broca's area (IBA), the fluency center of speech, and the superior temporal gyrus, the comprehension center, is related to the poor long-term outcome of aphasia in stroke. Between the 2 areas, Broca's area is more related to non-fluent aphasia, so this study was conducted based on the presence or absence of Broca's area involvement. Under the assumption that Broca's area involvement may influence the effect of rTMS on non-fluent aphasia after stroke, we investigated the difference in LF rTMS effect depending on Broca's area involvement in stroke patients with non-fluent aphasia.

MATERIALS AND METHODS

Study design and patients

This was a retrospective, single-center study. Patients were recruited based on the inclusion and exclusion criteria. The inclusion criteria were as follows: 1) initial stroke; 2) age between 18 and 80 years; 3) rTMS conducted within 1 year from the onset of stroke, between 2016 and 2019, and 4) non-fluent aphasia defined as a fluency score below 5 in the Korean version of the Western Aphasia Battery (K-WAB). The exclusion criteria were as follows: 1) previous rTMS therapy, 2) lack of MR brain images or K-WAB, 3) any previous brain lesion, and 4) disorders of consciousness. The patients were classified based on the IBA and non-IBA (NBA) groups, respectively. Broca's area is defined as Brodmann's area 44 (pars opercularis) and 45 (pars triangularis) [17]. To precisely localize Broca's area on MR imaging (MRI), MRI T1-weighted images were reoriented and normalized based on Montreal Neurological Institute (MNI) brain templates with SPM 12 software (University College London, London, UK).

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Lesions were selected, and MNI coordinates that were extracted by MRIcron (https://www.nitrc.org/projects/mricron) [16] were converted to Talairach coordinates using the Yale MNI to Talairach tool (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html) [18].

Assessment of aphasia

K-WAB was performed before and after rTMS. The K-WAB evaluations were performed by a speech-language pathologist. K-WAB is widely used to evaluate language function because of its consistency, validity, and reliability, and contains the same contents and structures as the WAB [19,20]. WAB is a useful tool for the classification of aphasia severity and aphasia types [21]. The WAB consists of 4 domains: fluency, comprehension, repetition, and naming. Kertesz's classification was used for aphasia classification [22]. Patients with fluency scores < 5 were classified as having non-fluent aphasia. Patients with comprehension scores > 4 were classified as having Broca's or cortical motor aphasia. Among them, patients with a repetition score < 8 had Broca's aphasia. Between global and isolation aphasias, patients with a repetition score < 5 were classified as having global aphasia. Aphasia quotient (AQ) was calculated using the following formula [22].

$$AQ = (\text{spontaneous speech} + \text{comprehension score}/20 + \text{repetition score}/10 + \text{naming score}/10) \times 2$$

Intervention

For every patient, one session of rTMS was applied every day for 10 working days by a medical technologist. All subjects were treated with a figure-of-8 coil using MagPro® (MagVenture Company, Farum, Denmark). The stimuli were applied to the right inferior frontal gyrus, which is a homologue in the right hemisphere of Broca's area. The stimulation site was localized by neuronavigation (TMS navigator, Localite, Germany) (**Fig. 1**). The resting motor threshold of the abductor pollicis brevis muscle was analyzed. The rTMS was conducted at 90% of the resting motor threshold with a 1 Hz frequency for 20 minutes, and a total of 1,200 pulses were delivered. After each session of rTMS, the patients underwent SLT for 30 minutes by another speech-language pathologist who had not performed K-WAB assessment. The SLT is a conventional speech therapy tailored to individual functions for non-fluent aphasia.

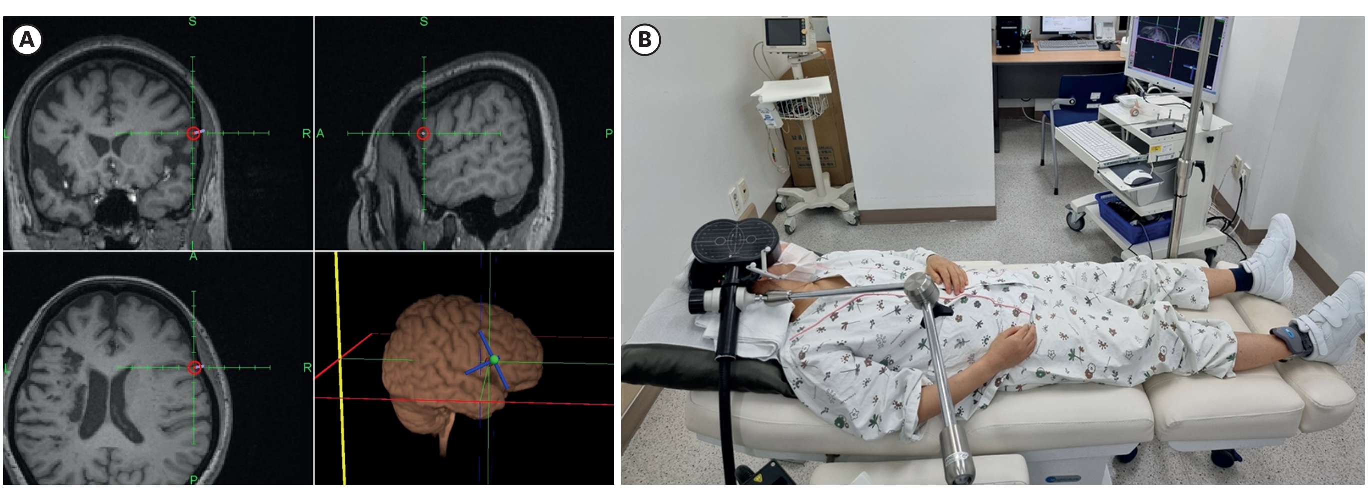

Fig. 1. (A) The repeated transcranial magnetic stimulation was applied to the right inferior frontal gyrus. (B) Stimulation was targeted using the neuronavigation system (a picture with informed consent from the patient).

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Statistical analysis

Chi-squared test was used to analyze the sex and type of aphasia. Mann-Whitney U test and Wilcoxon signed-rank test were used to analyze continuous variables. SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) was used, and a p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients

A total of 49 patients received rTMS treatment for aphasia between 2016 and 2019 in our rehabilitation center. Of these, 12 patients had previously received rTMS, 2 patients had no K-WAB assessment pre-or post-rTMS, 3 patients received the rTMS facilitation protocol, 1 patient had a traumatic brain injury, 6 patients were fluent aphasia, and 5 patients had more than 1 year of stroke onset. Finally, 29 patients were excluded and 20 patients were satisfied with the criteria for this study. Eighteen patients were men, and 2 were women. The rTMS was performed after an average of 4.90 ± 3.08 months from the onset of stroke. Thirteen patients had infarctions, and 7 had hemorrhages. Sixteen patients had global aphasia, 3 had Broca's aphasia, and one had transcortical motor aphasia. When divided into 2 groups according to the presence or absence of Broca's area involvement, 10 patients were assigned to each group. There were no statistical differences in age, sex, month of onset of rTMS, stroke type, and aphasia type between the 2 groups (**Table 1**).

Comparison of K-WAB pre- and post-rTMS in IBA and NBA groups

Comparing K-WAB conducted in pre-rTMS of IBA group and NBA group, there was no statistically significant difference in the AQ scores (p = 0.71). There were also no significant differences in fluency, comprehension, repetition, naming, and AQ (p = 0.94, p = 0.94, p = 0.12, and p = 0.32, respectively) (**Table 2**).

AQ scores significantly improved post-rTMS compared to pre-rTMS in total number of subjects and IBA and NBA groups (p < 0.01, p = 0.01, and p < 0.01, respectively; **Fig. 2A**). The characteristics of changes in the K-WAB sub-scores were not the same between the IBA and NBA groups. In the IBA group, comprehension, repetition, and naming increased significantly (p < 0.01, p < 0.01, and p = 0.04, respectively). However, fluency did not change

Table 1. Demographics of patients

	Total (n = 20)	IBA group (n = 10)	NBA group (n = 10)	p value*
Age (yr)	56.15 ± 11.73	59.40 ± 12.18	52.90 ± 10.90	0.22
Sex				0.47
Male	18	8	10	
Female	2	2	0	
Onset to rTMS (mon)	4.90 ± 3.08	5.17 ± 3.30	4.63 ± 3.00	0.71
Stroke type				1.00
Infarction	13	7	6	
Hemorrhage	7	3	4	
Types				0.51
Global	16	8	8	
Broca	3	2	1	
Mixed transcortical	0	0	0	
Transcortical motor	1	0	1	

Data are shown as mean ± standard deviation.
IBA, involvement of Broca's area; NBA, non-involvement of Broca's area; rTMS, repetitive transcranial magnetic stimulation.
*p value was derived from IBA and NBA.

Table 2. Korean version of the Western Aphasia Battery score comparison of IBA and NBA group

	IBA group	NBA group	p value
Pre			
AQ	17.77 ± 16.83	18.78 ± 13.41	0.71
Fluency	1.90 ± 1.73	2.00 ± 1.41	0.94
Comprehension	2.95 ± 2.33	2.59 ± 1.38	0.94
Repetition	0.99 ± 2.06	1.68 ± 2.67	0.12
Naming	1.15 ± 2.15	1.42 ± 1.80	0.32
Δ			
AQ	5.36 ± 5.13	7.25 ± 5.40	0.43
Fluency	0.30 ± 0.67	0.50 ± 0.97	0.59
Comprehension	0.71 ± 0.79	0.66 ± 0.87	0.91
Repetition	0.50 ± 0.51	0.52 ± 0.76	0.91
Naming	0.67 ± 1.14	0.75 ± 0.68	0.32

Data are shown as mean ± standard deviation.
IBA, involvement of Broca's area; NBA, non-involvement of Broca's area; AQ, aphasia quotient.

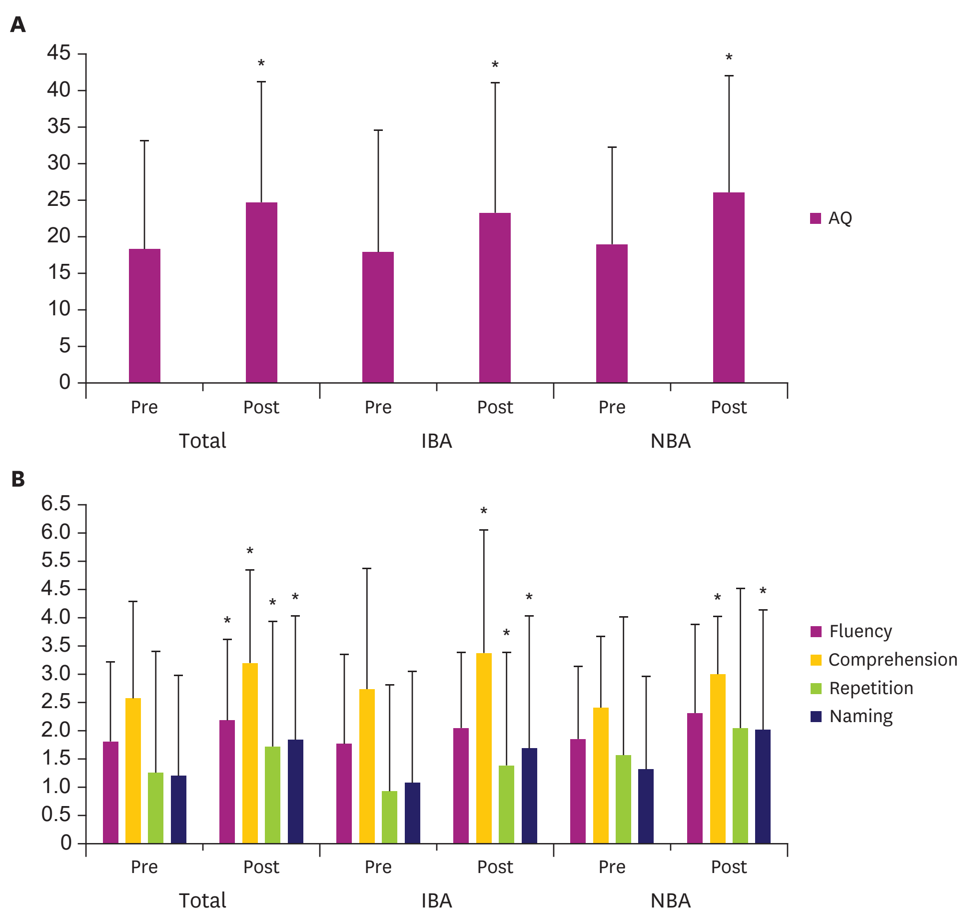

Fig. 2. K-WAB scores of pre-and post-repeated transcranial magnetic stimulation in total subjects, IBA and NBA groups. (A) Scores of AQ, (B) scores of fluency, comprehension, repetition and naming.
K-WAB, Korean version of the Western Aphasia Battery; IBA, involvement of Broca's area; NBA, non-involvement of Broca's area; AQ, aphasia quotient; rTMS, repeated transcranial magnetic stimulation.
*Asterisk means the difference of values of K-WAB is statistically significant compared to pre-rTMS ($p < 0.05$).

significantly ($p = 0.18$). Comprehension and naming increased significantly in the NBA group ($p = 0.02$ and $p = 0.01$, respectively). However, fluency and repetition revealed no improvement ($p = 0.13$ and $p = 0.07$, respectively) (**Fig. 2B**).

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Comparison of changes in K-WAB between IBA and NBA groups

There was no significant difference in the ΔK-WAB scores of AQ between the IBA and NBA groups ($p = 0.43$). The ΔK-WAB scores of fluency, comprehension, repetition, and naming also revealed no statistical difference between the 2 groups ($p = 0.59$, $p = 0.91$, $p = 0.91$, and $p = 0.32$, respectively; **Table 2**).

DISCUSSION

In this study, we investigated whether the effect of rTMS in patients with non-fluent aphasia was affected by Broca's area injury. For accurate analysis, MRI was standardized and grouped according to Broca's area damage, and K-WAB was used to evaluate language function. Further analysis was performed by evaluating the difference between pre- and post-rTMS, and then each score domain, such as fluency and repetition of K-WAB, were compared.

The AQ, fluency, comprehension, repetition, and naming of the K-WAB improved after rTMS in all subjects. The patients were divided into the IBA and NBA groups, and there was no significant difference in the change value of AQ, fluency, comprehension, repetition, and naming of the K-WAB.

In an earlier study, rTMS was performed in stroke patients without considering the type of aphasia [23]. The study participants were divided into the real rTMS and sham rTMS groups. Both groups exhibited significant improvement without any statistical difference between the groups in terms of improvement. The study reported that the therapeutic effect of rTMS was unclear. However, further analysis of the study findings suggests that rTMS is beneficial in patients with damage to the anterior part of the language area in the brain. LF rTMS studies were then conducted, focusing on non-fluent aphasia. In a previous randomized controlled study, spontaneous speech, auditory comprehension, naming, and aphasia AQ of WAB scores significantly improved in the LF rTMS group [11]. Another study comparing the LF rTMS and control groups reported an improvement in repetition and naming with no significant difference in other domains such as spontaneous speech, comprehension, and AQ [12]. Another study applying LF rTMS to more chronic non-fluent aphasia patients revealed improvement in the Concise Chinese Aphasia Test and its language production subsets [24]. Based on these studies, evidence-based guidelines on the therapeutic use of rTMS suggest that LF-rTMS has evidence of probable efficacy in patients with non-fluent aphasia [7]. In accordance with this guideline, LF rTMS was also applied to non-fluent aphasia patients in our clinic. It was found that fluency, comprehension, repetition, naming, and AQ improved through the K-WAB pre- and post-rTMS in post-stroke non-fluent aphasia patients.

Several studies have investigated the effect of brain lesions on motor impairment in post-stroke patients, where rTMS has been the most studied. In a meta-analysis of rTMS on motor function after stroke, the lesion site subgroup analysis revealed a relatively larger effect size in patients with subcortical stroke when compared with non-specified lesion sites. They concluded that rTMS was more effective in motor function with subcortical stroke [25]. Studies related to the effect of rTMS on aphasia in stroke patients are fewer than those on motor impairment, and there is a lack of studies on lesion-related effects in post-stroke aphasia.

In our study, we classified the groups based on the IBA to determine whether there were differences in the effects of rTMS in non-fluent aphasia after stroke. As a result, there was

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no difference in the effect of rTMS on improving aphasia according to the presence or absence of Broca's area. A previous study had a similar aim as that of ours. Zumbansen et al. [26] reported a randomized trial of non-invasive brain stimulation for subacute post-stroke aphasia and a subgroup analysis for lesion location (affecting Broca's area or not). The study showed that LF rTMS significantly improved language abilities in patients with intact Broca's area, but not in patients with damage in this region. This study reported results that were different from that of our study, and the subjects were slightly different from that of ours. They performed a study on post-stroke aphasia regardless of the type, but we limited the study to non-fluent aphasia, which is known to have positive effects of LF rTMS. We hypothesized that different study subjects influence different outcomes.

In our study, we found that there were no significant differences in effectiveness with respect to the IBA or NBA in post-stroke non-fluent aphasia. Therefore, we suggest that although the IBA is a poor prognostic factor for aphasia, its involvement should not be considered an inferior effect factor when rTMS is applied to non-fluent aphasia in stroke patients.

This study is meaningful in that it analyzed LF rTMS responses based on Broca's area involvement in non-fluent post-stroke aphasia. However, there are some limitations to our study. First, the sham control group was not included in the present study. Based on our research, it is necessary to conduct studies with a sham group. Second, this was a retrospective study, and the number of patients was less. Although there was no statistical difference in the underlying characteristics between the groups of patients, a relatively small number of female patients and a small number of patients may have affected the outcome. Third, long-term follow-up was not conducted. Fourth, only Broca's area was considered to confirm the lesion-dependent treatment effect in our study. Although it is known that Broca's area is the motor center of speech, studies on the anatomical regions affecting the recovery of non-fluent aphasia patients are still lacking. Therefore, further study is warranted with more subjects with non-fluent post-stroke aphasia, which should include a sham group and analysis of various stroke lesions.

In conclusion, we compared stroke patients with non-fluent aphasia who underwent LF rTMS depending on the IBA. The results of this study revealed that LF rTMS contributes to the improvement in post-stroke aphasia, irrespective of the IBA. Therefore, LF rTMS could be a treatment option for non-fluent post-stroke aphasia, regardless of the IBA.

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