The new technology of repetitive transcranial magnetic stimulation (rTMS) has been suggested to be capable of promoting neuroplasticity pertaining to language recovery after stroke. Whether recovery from chronic aphasia involves either ipsilesional residual cortical reorganization or contralateral neuroadaptation remains unclear; but as the growing body of research has demonstrated, inhibitory rTMS applied to the contralesional cortex can successfully facilitate language recovery. It is hypothesized that this contralesional neuro-modulation improves long-term communication outcomes by alleviating transcallosal disinhibition and after the paradoxical functional facilitation principle, whereby disruption of brain activity by TMS might lead to functional facilitation mediated through distant cortical or subcortical connections.

Recent advances in the use of the rTMS strategy have highlighted the benefit of a combined use-dependent learning program coupled with rTMS priming. Such rTMS modulation consolidates induced long-term potentiation–like or suppression-like effects when it is applied over an area that is subsequently activated by the corresponding task practiced.

Patients with nonfluent aphasia showed substantial improvement when subsequent speech training was combined with a priming rTMS protocol. The efficacy of a clinical protocol involving simultaneously administering these remedies to aphasic patients remains undetermined. Motor training incorporated concurrently into an excitatory rTMS session was found to facilitate motor recovery that could not be obtained by either remedy alone after a single intervention. Using a direct transcranial electric current, simultaneous physiotherapy was executed during the conditioning course and demonstrated a favorable outcome, compared with sham stimulation combined with physiotherapy. On the basis of this model, the new technology of repetitive transcranial magnetic stimulation (rTMS) may facilitate recovery after stroke, the efficacy of synchronous speech therapy integrated with an rTMS protocol has yet to be determined. We investigated language responses to this strategy and determined the longevity of the resulting therapeutic outcomes.

Background and Purpose—Although multiple studies have suggested that repetitive transcranial magnetic stimulation (rTMS) may facilitate recovery after stroke, the efficacy of synchronous speech therapy integrated with an rTMS protocol has yet to be determined. We investigated language responses to this strategy and determined the longevity of the resulting therapeutic outcomes.

Methods—Forty-five patients with stroke who presented with nonfluent aphasia were randomly assigned to the TMS syn group and underwent synchronous picture-naming training together with contralesional 1 Hz-rTMS for 10 daily sessions. The TMS sub group underwent subsequent picture-naming activity after the primed 1 Hz-rTMS, and the TMS sham group received concurrent naming task along with the sham 1 Hz-rTMS. The Concise Chinese Aphasia test and the picture-naming test were performed before, immediately, and after 3 months of the intervention.

Results—TMS syn showed significantly superior results in Concise Chinese Aphasia test score (P<0.001), expression and description subtests (P<0.001), and action (P=0.02) and object naming activity (P=0.008); the superior results lasted for 3 months (P=0.005), in comparison with the TMS sub and TMS sham groups.

Conclusions—We established a real-time model that involved implementing verbal tasks together with the rTMS protocol. Our results confirmed that the strategy yielded favorable outcomes that were of considerable longevity. The results also indicated that the rTMS protocol and language training can be combined to achieve outcomes superior to those obtained when used separately.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02120508. (Stroke. 2014;45:00-00.)

Key Words: aphasia • repetitive transcranial magnetic stimulation • stroke
which pertains to a motor training program, online speech therapy during rTMS modulation should augment language learning. Given the proposed Hebbian learning principle, which emphasizes spike timing–dependent neuroplasticity,11 we hypothesized that temporal synchronous modulation (online model) in the Broca area through rTMS modulation and concurrent language system activation can result in greater synaptic strength than the separate application of these interventions (offline model).

We investigated the efficacy of low-frequency rTMS coupled with a simultaneous picture-naming activity for treating chronic nonfluent aphasic patients and evaluated the resulting effects for a 3-month period.

Methods

Participants

Seventy-six patients with stroke who were admitted to the stroke unit of a tertiary medical center or who attended follow-up visits at outpatient clinics were evaluated consecutively for participation in this study. Three patients approached declined to participate (Figure 1); and 45 right-handed patients met the inclusion criteria: (1) a diagnosis of nonfluent aphasia resulting from a first-ever left middle cerebral artery infarction that had been confirmed by MRI; (2) >6 months of poststroke duration with a plateau in aphasic condition; (3) no current depression as evaluated using the Aphasic Depression Rating Scale12; (4) an absence of spatial neglect or visual field deficits; and (5) an absence of TMS contraindications. Forty-three patients completed the 3-month assessment. The study was approved by the local institutional review board, and all patients gave their written informed consent before participating.

The biographical data of the enrolled patients (5 women and 40 men aged 41–78 years) are shown in Table 1. The types of aphasia for all patients consisted of the Broca type (n=22), transcortical-motor type (n=19), and global aphasia with mild comprehensive deficits (n=4); these patients presented with a mean Concise Chinese Aphasia test (CCAT) score of 7.3 points.

Design

We conducted a sham-controlled, double-blind parallel study (Figure 1). After random group assignment conducted using opaque numbers in concealed envelopes, the 45 patients were assigned to 3 groups, each of which comprised 15 patients. Each individual received either real or sham 1-Hz rTMS over the Broca homologous (ie, contralateral pars triangularis, PTr) for 20 minutes. The patients in the TMSsyn group underwent real 1 Hz–rTMS coupled with a synchronous picture-naming task for 10 daily sessions (offline model), whereas patients in the TMSsham group underwent real 1 Hz–rTMS followed by a picture-naming activity for 20 minutes in 10 daily sessions (offline model). Patients in the TMSsham group received sham 1-Hz rTMS combined with a 20-minute concurrent naming activity for 10 daily sessions. Each patient underwent a 60-minute session involving speech training twice a week that was administered by a speech-language pathologist who was blind to the patient’s group assignment. Communication skills were evaluated before treatment (baseline), after completion of the treatment (post 1), and 3 months after the intervention (post 2).

Determining the Stimulation Target

Before TMS conditioning, all patients underwent 3-Tesla structural MRI. The individual MRI films were uploaded onto a frameless stereotaxic system (Brainsight; Rogue Research, Montreal, Canada) to coregister the stimulation locus related to the anatomic marks of the patient’s head by using a real-time feedback presentation of the images. The target (contralateral PTr) was defined ventrally by the horizontal ramus of the Sylvian fissure and caudally by the vertical ramus of the Sylvian fissure (homologous to the left dorsal anterior PTr).11 Each stimulation site was tagged to the MRI for subsequent sessions.

Determining the Resting Motor Threshold

We performed TMS using Magstim Rapid2 (Magstim Company, Withland, Dyfed, United Kingdom) through a 70-mm figure-8 coil. Each patient sat in a reclining armchair with both hands supported and kept their eyes open. To activate the corticospinal tract most efficiently, the coil was operated tangentially to the scalp and rotated 45° away from the sagittal midline. The resting motor threshold for the contralateral first dorsal interosseous, as the minimal intensity, was determined to be that at which motor evoked potential of at least an amplitude of 100 μV could be elicited in at least half of 10 consecutive trials.21 A Dantec Keypoint electromyograph (Dantec, Skovlunde, Denmark) was connected to the stimulator to record the motor evoked potential signals of the first dorsal interosseous. The amplified (100 μV to 1 mV/div) and bandpass-filtered (20–2000 Hz) signals were digitized at a 20 kHz sampling rate.

Figure 1. Outline of the study design in the form of a flowchart; recruitment, group allocation, allocation treatment, follow-up, and analysis are depicted. rTMS indicates repetitive transcranial magnetic stimulation.
rTMS Protocol and Integrated Tasks
Twelve hundred pulses comprised the 1-Hz rTMS training; these pulses were 90% of resting motor threshold and were applied over the contralesional target area for 20 minutes. This paradigm was used in a previous study and was demonstrated to be useful in improving naming ability. We used a placebo coil (Magstim Co) set with an identical paradigm to the TMSsham for the sham stimulation.

During rTMS conditioning, patients in the TMSsyn and TMSsham groups sat in front of a computer monitor displaying image stimuli in series. A therapist controlled the stimulus display and instructed the patients to name the object or action figures explicitly and loudly. The stimuli used in the action and object-naming task were taken from the International Picture Naming Database. We attempted to challenge the expressive capacity of patients by providing an optimal level of difficulty. Each illustration appeared for a maximal response time of 20 ss; after that, the answer was provided to the patient by earphones. Although rTMS-induced facial muscle twitches could slightly compromise precise articulation, the patients were allowed to adapt to this involuntary movement before participation and practiced speaking under such circumstances. Members of the TMSsub group were instructed to perform a 20-minute naming task immediately after real 1-Hz rTMS conditioning.

Assessing Language Function
An independent speech language pathologist blind to the patient allocation evaluated their language function before the first intervention session, on the day of the 10th session, and 3 months after the last intervention session, by using the CCAT. Three subcategories related to language production were assessed: (1) conversation (Conv), (2) describing a family picnic picture (Desp), and (3) naming objects and their use (Exp). CCAT scores were calculated by averaging the scores of each subtest, which ranged from 0 (minimum) to 12 (maximum). We also recorded the rate of correct answers in response to 20 objects and 20 action pictures; these were selected from the International Picture Naming Database and were matched for familiarity, frequency, visual complexity, and agreement measures to enable measurement to be repeated at the 3 evaluation points. The content of the test pictures did not duplicate the training material. Phonetic error, phonemic errors, paraphasia, and neologism were scored as incorrect responses.

Speech Therapy
All participants received a 60-minute training program administered by a speech-language pathologist shortly after the intervention program twice a week. The training program emphasized verbal expressive skills, including repetition, phonemic training, semantic training, naming, conversation, picture-description tasks, and phrase-generation tasks. Other compensatory modalities, such as gestures, drawing, and the intonation of melodies, were prohibited during the training course and self-learning activity.

Statistics
The baseline assessments and biographical data were compared between the groups using a 1-way analysis of variance for continuous data and a χ² test for categorical data as appropriate. To determine improvements in CCAT score and naming accuracy rate, the Wilcoxon signed-rank test was used for intragroup comparison; repeated-measure analysis of variance was used for intergroup comparisons; time was the withinsubject factor and the group was the betweensubject factor. A post hoc pairwise comparison was performed using the Bonferroni procedure. The level of significance was set at P<0.05. Changes in scores (ie, the outcome value minus the baseline value) were calculated and expressed as a percentage compared with the baseline.

Results
We observed no differences between the groups in baseline features, such as time poststroke, aphasia type, CCAT score, and education level (P>0.05; Table 1). One patient in the TMSsham group reported a dull pain at first when placed under the activated coil, but their discomfort subsided once the stimulation intensity was reduced by 5%.

Improvement for Each Group
Compared with the baseline, TMSsyn exhibited significant improvement on all language tests, including total CCAT score (P<0.001), subtests of Conv (P<0.001), Desp (F=0.002), and Exp (P=0.001), action-naming accuracy (P=0.011), and object-naming accuracy (P=0.005) at post 1, as well as in total CCAT score (P=0.003), Exp (P=0.019), action-naming accuracy (P=0.006), and object-naming accuracy (P=0.003) at post 2. After asynchronous neurostimulation, TMSsham was associated with significant improvement in CCAT score both at post 1 (P=0.004) and post 2 (P=0.017), and Conv (P=0.014) at post 1. After 2 weeks of traditional speech therapy, TMSsham demonstrated improvement in action-naming accuracy (P=0.046) at post 1 and object-naming accuracy at post 2 (with a borderline significance of P=0.059), but not in CCAT score or subtests. The percentage of improvement in CCAT score and subtests for each group are shown in Figure 2.

Intergroup Comparison CCAT Assessment
At post 1, the CCAT score (F=23.9; P<0.001) and subtests revealed significant intergroup differences for Conv (F=5.7; P=0.007), Desp (F=10.1; P<0.001), and Exp (F=5.5; P<0.001). Post hoc analysis indicated that TMSsyn exhibited the most prominent improvement in the CCAT score (F=23.9; P<0.001), Desp (F=10.1; P<0.001), and Exp (F=15.5; P=0.001) relative to TMSsham (Table 2; Figure 2). The differential effects also exhibited between the TMSsyn and...
TMSsham results, namely Conv ($F_{[2,42]}=3.2; \ P=0.043$), Desp ($F_{[2,42]}=4.6; \ P=0.012$), and Exp ($F_{[2,42]}=4.9; \ P=0.01$).

Intergroup Comparison Picture-Naming Test

Post hoc analysis revealed that the TMS syn group showed superior action and object naming ability compared with the TMS sub group ($F_{[2,42]}=6.3, \ P=0.02$; $F_{[2,42]}=9.1, \ P=0.008$, respectively) and the TMS sham ($F_{[2,42]}=6.3, \ P=0.003$; $F_{[2,42]}=9.1, \ P=0.001$, respectively) at post 1 (Table 2; Figure 3). At post 2, the differential effect between TMS syn and TMS sub remained significant, as shown in object-naming accuracy ($F_{[2,42]}=7.83; \ P=0.005$) and action-naming accuracy ($F_{[2,42]}=4.81; \ P=0.042$).

**Discussion**

We investigated how the concurrent naming task, combined with suppressive rTMS, affected language output among chronic nonfluent aphasic patients. This double-blind study

<p>| Table 2. Mean Group Data (±SD) of CCAT Scores and Naming Tests for Each Group After Repetitive Transcranial Magnetic Stimulation Interventions |
|---------------------------------|---------------------------------|---------------------------------|
|                                | <strong>TMS syn Group</strong>              | <strong>TMS sub Group</strong>              | <strong>TMS sham Group</strong>             |</p>
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post 1</th>
<th>Post 2</th>
<th>Baseline</th>
<th>Post 1</th>
<th>Post 2</th>
<th>Baseline</th>
<th>Post 1</th>
<th>Post 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCAT score</td>
<td>6.6±2.2</td>
<td>8.2±2.0†</td>
<td>8.4±1.9</td>
<td>6.6±2.4</td>
<td>7.1±2.4</td>
<td>8.0±2.2</td>
<td>6.6±2.9</td>
<td>6.5±3.1</td>
<td>6.4±3.1</td>
</tr>
<tr>
<td>Conversation</td>
<td>7.3±2.5</td>
<td>8.4±2.2†</td>
<td>8.4±2.3†</td>
<td>6.9±2.9</td>
<td>7.4±3.0</td>
<td>7.3±3.0</td>
<td>7.0±3.3</td>
<td>7.1±3.4</td>
<td>6.4±3.2</td>
</tr>
<tr>
<td>Description</td>
<td>5.4±2.2</td>
<td>6.7±2.2†</td>
<td>7.1±2.5†</td>
<td>5.0±2.2</td>
<td>5.2±2.3</td>
<td>6.4±2.7</td>
<td>5.2±2.7</td>
<td>5.1±2.7</td>
<td>4.6±2.9</td>
</tr>
<tr>
<td>Expression</td>
<td>6.5±2.3</td>
<td>8.5±2.3†</td>
<td>8.5±2.3†</td>
<td>6.4±2.7</td>
<td>6.9±2.8</td>
<td>7.1±3.0</td>
<td>6.5±3.1</td>
<td>6.3±3.2</td>
<td>5.8±2.4</td>
</tr>
<tr>
<td>Object naming accuracy, %</td>
<td>40.5±20.1</td>
<td>60.5±20.8†</td>
<td>66.6±21.3†</td>
<td>43.8±18.7</td>
<td>47.7±16.1</td>
<td>47.7±20.8</td>
<td>42.3±17</td>
<td>41.6±20</td>
<td>45.5±19.7</td>
</tr>
<tr>
<td>Action naming accuracy, %</td>
<td>36.6±18</td>
<td>46.6±18.4†</td>
<td>53.8±14.5†</td>
<td>30.5±18.2</td>
<td>33.8±12.3</td>
<td>35.5±14.7</td>
<td>34.6±16.1</td>
<td>32±12.2</td>
<td>36.5±12.0</td>
</tr>
</tbody>
</table>

CCAT indicates Concise Chinese Aphasia test; and TMS, transcranial magnetic stimulation.

†$P<0.05$, post hoc analysis.

*Significant difference between TMS syn and TMS sub.

†Significant difference between TMS syn and TMS sham.
Results from Barwood et al.1,18 demonstrated persistent language improvement in nonfluent aphasia for 2 to 8 months after 1-Hz rTMS conditioning. In another study conducted by Weiduschat et al.,8 PET scans showed an amelioration in right PTr overactivity in patients who received real rTMS, which was followed by greater linguistic gains in contrast with those who received the control rTMS over the vertex. Suppressing the right PTr may promote the function of the right pars opercularis through U fibers, which connect these 2 adjacent gyri, as was demonstrated in diffusion tensor imaging tractography.7,19 The right pars opercularis has been shown to play a causal role in controlling articulation and phonation; along with the ventral premotor cortex, pars opercularis permits enhanced modulation of the remaining bilateral dorsal language network through the arcuate fasciculus and mirror neuron system.26 These results provide a rationale for using low-frequency rTMS for treating chronic aphasic patients.

Adjunctive speech therapy after each rTMS session was recently reported to optimize the effects of the TMS protocol.22,23 Molecular evidence of brain plasticity has indicated that physiological demands remodel cortical organization and that learning-directed training stimulates corresponding functional recovery, which leads to evolutionary neuroplasticity.22,23 Although Naeser et al.7 observed that low-frequency rTMS coupled with subsequent speech therapy exerted a profound influence on language skills in nonfluent aphasia patients, little is known about the usefulness of rTMS with simultaneous language-behavior training in facilitating language recovery.

The Hebbian theory posits that the simultaneous activation of neuron cells leads to increased synaptic strength through associated learning and convergent sensorimotor input in the target cortical area.11,24–26 Such a Hebbian rule could consolidate an long-term potentiation–like effect in the motor system24,25 or in the somatosensory system.27 Our results are consistent with prior indications that magnetic stimulation, paired with synchronous visual stimulation and naming execution, is hypothesized to facilitate long-term potentiation–like induction and cause additional effects. These may have a possible mechanism involving enhanced synaptic drive and a spike timing–dependent plasticity. Two features of long-term potentiation association and input specificity are compatible with the present design and findings: namely, they could result from posttranslational modification of the Na+ and K+ channels and from N-methyl-D-aspartic acid receptor activity, which secondarily influence membrane depolarization profiles among neurons.26 The engaged verbal task was designed to enhance goal-directed learning efficacy in response to activated neurotransmitters or neurosynaptic excitation derived from rTMS modulation.

To promote verbal expression and naming performance, we used suppressive rTMS applied over the contralesional PTr based on conclusions drawn from a meta-analysis that indicated that poststroke recruitment of this area may hinder language recovery.4 Although a diverse strategy using excitatory rTMS over the perilesional frontal cortex was described as a promising method for language recovery,3 we did not favor this rTMS protocol because of the possibility that administering high-frequency rTMS might induce speech arrest during language production.24 In our experiment, we did not observe any speech arrest or speech difficulty when using a low-frequency setting. The exact mechanism underlying the neuroplasticity associated with the current strategy is unknown because of lack of neuroimaging and other electrophysiological evidence. Neuroimaging studies conducted pre-rTMS and post-rTMS can provide microstructural and neurophysiological evidence.24,26,27
information that can facilitate an understanding of longitudinal neuroplasticity and how it is related to language recovery. Whether a broader, unexpected effect may be elicited in other linguistic domains and neuropsychological aspects deserves further comprehensive study.

Among the CCAT subtests, the most prominent differences between the TMS_{sham} and TMS_{sub} groups emerged in describing family picnic pictures (Desp) and expressing the use of an object (Exp). These subtests measure complex verbal production related to word retrieval and output. They may have had a greater sensitivity and ability to differentiate the additional linguistic gain derived from the synchronous protocol, and thus, the alterations in these subtests may have inadequate longevity measured at 3 months post intervention. By contrast, the superior modulating effect measured with the naming test was found to persist 3 months after the synchronous protocol. This discrepancy indicated that the optimal number of sessions and the optimal duration of induced-paired therapy have not yet been determined. A recent research described an advanced protocol that comprised 20 consecutive sessions. This was demonstrated to be both safe and effective in boosting motor facilitating efficacy compared with traditional 10-session rTMS. However, a safe, optimal repetition number, and appropriate rest interval for aphasic patients remains uncertain. With regard to this combined therapy, establishment of an optimal conditioning protocol is important, and further dosage studies should be conducted.

Our finding that the TMS_{sub} group exhibited significant improvement after rTMS modulation compared with the baseline levels was consistent with Naeser’s finding that additional improvement may be obtained when rTMS is followed immediately by language therapy. However, the language outcome of the TMS_{sham} group did not significantly differ from that of the TMS_{sub} group in this study. This could be attributable to the incorporation of the 20-minute naming activity that was not as effective as the 3-hour constraint-induced language therapy in augmenting the rTMS after-effects, as reported by Martin et al.

This study provides encouraging results related to language recovery among patients with chronic aphasia. Language performance can be augmented by online verbal training and rTMS modulation, which expands neurorehabilitation clinical practice. This potential strategy could be modified either by using computer-embedded training or by incorporating virtual reality, either or both of which might augment training efficacy. This integrative method could be applied as a complementary aphasia therapy performed in conjunction with traditional language treatment.

Acknowledgments
We thank Eric Chuang for editing assistance with this article.

Sources of Funding
This work was supported by the Ministry of Science and Technology grant of Taiwan (1032314B075059MY3).

Disclosures
None.

References


Efficacy of Synchronous Verbal Training During Repetitive Transcranial Magnetic Stimulation in Patients With Chronic Aphasia

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Stroke. published online November 6, 2014;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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