Video Article

Utilizing Repetitive Transcranial Magnetic Stimulation to Improve Language Function in Stroke Patients with Chronic Non-fluent Aphasia

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URL: http://www.jove.com/video/50228
DOI: doi:10.3791/50228

Keywords: Medicine, Issue 77, Neurobiology, Neuroscience, Anatomy, Physiology, Biomedical Engineering, Molecular Biology, Neurology, Stroke, Aphasia, Transcranial Magnetic Stimulation, TMS, language, neurorehabilitation, optimal site-finding, functional magnetic resonance imaging, fMRI, brain, stimulation, imaging, clinical techniques, clinical applications

Date Published: 7/2/2013

Citation: Garcia, G., Norise, C., Faseyitan, O., Naeser, M.A., Hamilton, R.H. Utilizing Repetitive Transcranial Magnetic Stimulation to Improve Language Function in Stroke Patients with Chronic Non-fluent Aphasia. *J. Vis. Exp.* (77), e50228, doi:10.3791/50228 (2013).

Abstract

Transcranial magnetic stimulation (TMS) has been shown to significantly improve language function in patients with non-fluent aphasia[1]. In this experiment, we demonstrate the administration of low-frequency repetitive TMS (rTMS) to an optimal stimulation site in the right hemisphere in patients with chronic non-fluent aphasia. A battery of standardized language measures is administered in order to assess baseline performance. Patients are subsequently randomized to either receive real rTMS or initial sham stimulation. Patients in the real stimulation undergo a site-finding phase, comprised of a series of six rTMS sessions administered over five days; stimulation is delivered to a different site in the right frontal lobe during each of these sessions. Each site-finding session consists of 600 pulses of 1 Hz rTMS, preceded and followed by a picture-naming task. By comparing the degree of transient change in naming ability elicited by stimulation of candidate sites, we are able to locate the area of optimal response for each individual patient. We then administer rTMS to this site during the treatment phase. During treatment, patients undergo a total of ten days of stimulation over the span of two weeks; each session is comprised of 20 min of 1 Hz rTMS delivered at 90% resting motor threshold. Stimulation is paired with an fMRI-naming task on the first and last days of treatment. After the treatment phase is complete, the language battery obtained at baseline is repeated two and six months following stimulation in order to identify rTMS-induced changes in performance. The fMRI-naming task is also repeated two and six months following treatment. Patients who are randomized to the sham arm of the study undergo sham site-finding, sham treatment, fMRI-naming studies, and repeat language testing two months after completing sham treatment. Sham patients then cross over into the real stimulation arm, completing real site-finding, real treatment, fMRI, and two- and six-month post-stimulation language testing.

Video Link

The video component of this article can be found at http://www.jove.com/video/50228/

Introduction

Aphasia-an acquired deficit of language ability-is a common and often debilitating consequence of stroke[2]. Although some degree of recovery from aphasia after acute stroke is typical, many patients experience at least some degree of persistent deficits, and existing language therapies are generally considered to be only modestly effective in facilitating recovery[3-5]. Recent years have seen the emergence of noninvasive stimulation techniques such as transcranial magnetic stimulation (TMS) as promising potential treatment approaches for a variety of deficits after stroke, including aphasia. TMS employs the principle of electromagnetic induction and involves the generation of a rapidly fluxing magnetic field in a coil of wire. When the coil is placed adjacent to the head of a subject, the magnetic field penetrates the scalp and skull, inducing a current in underlying cortical neurons that is sufficient to depolarize neuronal membranes and generate action potentials[3]. TMS parameters such as frequency, intensity, and number of pulses can be varied in order elicit different neurophysiologic, behavioral, and perceptual effects[4,5]. Repetitive TMS (rTMS) entails the administration of a series of pulses at a predetermined frequency and produces effects that can outlast the application of the stimulation. Germane to the current experiment, evidence shows that rTMS delivered at a low frequency (0.5-2 Hz) tends to focally decrease cortical excitability, while high-frequency stimulation has been associated with cortical excitation[3]. rTMS has been explored as a treatment for various neurologic and psychiatric disorders, most notably depression[6].

A growing body of evidence suggests that low frequency rTMS may be used to enhance language recovery in persons with chronic stroke-induced aphasia. Naeser and colleagues[7,8] were the first to apply 1 Hz inhibitory rTMS to the right inferior frontal gyrus for 20 min five days a week for two weeks in four right-handed patients with chronic non-fluent aphasia. Significant improvements in naming were observed, which persisted for at least eight months following completion of stimulation[8]. We subsequently replicated and extended these results, and have

demonstrated that 1 Hz stimulation resulted in persistent improvements in both naming and spontaneous elicited speech in chronic non-fluent aphasic patients[9-11]. Encouragingly, the results of small studies such as these have been replicated in further investigations in patients with chronic stroke[12], as well as in patients with subacute stroke and aphasia[13].

One important and nearly ubiquitous feature of prior TMS studies in patients with non-fluent aphasia is that the salutary effects of stimulation appear to be site-specific. Adopting the approach initially employed by Naeser and colleagues, most investigations in which rTMS has been used to facilitate language recovery have targeted the right pars triangularis[1] (Brodmann area 45). In fact, recent evidence has suggested that stimulation of other regions of the right inferior frontal gyrus may be ineffective, or may even have deleterious effects on language performance[14], underscoring the need for careful individual identification of optimal stimulation sites.

Building upon the approach established by Naeser and colleagues[8], our ongoing investigation explores the effects of inhibitory rTMS in the inferior frontal gyrus on language ability, and also examines the topographic specificity of rTMS effects in the right frontal lobe. In this article, we provide a detailed description of how an optimal site for stimulation can be identified in patients with chronic non-fluent aphasia. We then describe the administration of therapeutic rTMS and explain our techniques for assessing the efficacy of stimulation in enhancing language recovery in this population.

Protocol

1. Pre-Treatment Evaluation

1. Recruit patients who meet the eligibility requirements for the study. These criteria include a single, unilateral, left hemisphere ischemic stroke that spares the supplementary motor area (SMA), mild to moderate non-fluent speech (defined as the ability to produce meaningful words and at least a 2-4 word length string), between the ages of 18 and 75 and at least six months post-stroke.
2. Additionally, all potential patients must be able to name at least three of the first 30 items on the Boston Naming Test[15], an average of at least three pictures out of 20 when presented with ten sets of picture-naming stimuli taken from the Snodgrass and Vanderwart corpus[16], and score at or above the 25th percentile on the subtests for word comprehension and commands on the Boston Diagnostic Aphasic Examination[17].
3. Conduct a medical screening examination to ensure patients are healthy enough to participate in the study, and that there are no contraindications to undergoing a Magnetic Resonance Imaging (MRI) scan or TMS.

2. Baseline Testing

1. Administer a battery of standardized tests on three separate days to assess the extent of each patient's language impairment and deficits in other cognitive domains. The tests include the Cookie Theft picture description subtest of the BDAE[18], BDAE (2nd Ed.) Subtests for Word Comprehension (Basic Word Discrimination) and Commands, Boston Naming Test[15], sets of 40 line drawing stimuli taken from the Snodgrass and Vanderwart picture database[16], and the Cognitive Linguistic Quick Test[19] (CLQT).
2. Initiate a baseline BOLD-fMRI study in which the patient performs a picture-naming task with oral response. Collect high resolution whole-brain T1-weighted images with a MPRAGE sequence (RT = 1,620 msec, TE = 3.87 msec, FA = 15, FOV = 192 x 256, slices = 160, voxel sizes = 1 mm^3). Acquire functional volumes using a whole-brain T2*-weighted BOLD echoplanar sequence (TR = 3,000 sec, TE = 35 msec, FA = 90, FOV = 128 x 128, slices = 31, voxel sizes = 1.875 mm^2, slice thickness = 4 mm).
3. Randomize patients into either a group receiving real repetitive TMS (rTMS) or a group receiving initial sham stimulation (sTMS), followed by rTMS **(Figure 1)**.

3. Identification of Optimal Sites of Stimulation

1. In order to target rTMS to cortical sites in a precise and accurate manner, use a neuronavigational system (*e.g.* Brainsight, Rogue Research, Montreal) to co-register high-resolution whole-brain T1-weighted images (see 2.2 above) with the location of the patient and coil. For the rTMS group, determine resting motor threshold (RMT) via stimulation to right motor cortex and subsequent visual inspection[20].
2. During real rTMS, orient the coil with the handle in a posterior and inferior direction approximately 45° clockwise from the downward position. For the sham group, administer sTMS with the coil perpendicular to the head so that only the outer rim of the lateral wing of the coil contacts the head. In this orientation, the peak magnetic field runs parallel to the skull and thus does not produce cortical stimulation.
3. In six separate sessions conducted over five days (two sessions conducted on final day, with a 45-minute break in between sessions), administer ten minutes of either rTMS (600 pulses of 1 Hz at an intensity of 90% RMT) or sTMS to different sites in the right inferior frontal lobe: the primary motor cortex (M1) corresponding to the mouth, pars opercularis (BA 44), anterior pars triangularis (BA 45), dorsal posterior pars triangularis (BA 45), ventral posterior pars triangularis (BA 45), and pars orbitalis (BA 47; **Figure 2**). Randomize stimulation site order between patients.
4. Have patients perform a 40-item picture-naming task immediately before and after each TMS session. Picture stimuli are taken from the Snodgrass and Vanderwart[16] item set, the Peabody Picture Vocabulary Test[21], and the International Picture Naming Project (IPNP) database[22]. The 40-item lists must be matched with respect to word length, frequency, and semantic category; in our item lists 20 items were novel while 20 were repeated throughout the testing sessions to assess for practice effects. Utterances should be counted as correct if they differ from the target by no more than one phoneme[8]. Word list order should be randomized across subjects and each subject should receive different word lists at every visit.
5. Determine the optimal site of stimulation by performing one-sample *t*-tests comparing the change in picture-naming performance at each site to the mean change in naming performance for all other sites. Next, compare the change in performance at the optimal site to the variance of performance across all six pre-rTMS sessions; if the change in performance after rTMS is greater than two times the standard deviation of mean pre-TMS performance, it is unlikely that the benefit in naming performance is attributable to test-retest variability[9].

6. For sham site-finding, administer sTMS over the pars triangularis. This location acts as the "optimal site" for the sham arm of the treatment phase, as described in Protocol section 4.

4. Treatment Phase

1. Administer rTMS or sTMS to the optimal stimulation site for ten days in a twelve-day period (stimulation on every weekday with weekends off).
2. On the first day of stimulation, the order of events is as follows: have the patient undergo an fMRI (with concurrent picture-naming, as in baseline), administer the 40-item naming task, stimulate the optimal site using 20 min of either 1 Hz rTMS at 90% RMT or sTMS, administer the naming task again, and finally have the patient undergo a second fMRI with concurrent picture-naming.
3. On days two through nine, the protocol consists of a 20-minute rTMS session (1,200 pulses), using 1 Hz rTMS at 90% RMT or sTMS.
4. On day ten, stimulate the optimal site for 20 min with 1 Hz rTMS, preceded and followed by the picture-naming task. Of note, picture item lists shown on days one and ten should be different, but matched for frequency, word length, and semantic category as noted above.

5. Two- and Six-month Follow-up Visits

1. Two months following day ten of either rTMS or sTMS, repeat baseline testing (step 2.1), as well as fMRI with concurrent picture-naming.
2. Patients in the sham condition should then cross over to real TMS condition, beginning with the optimal site-finding phase **(Figure 1)**.
3. Six months following day ten of real rTMS stimulation, repeat baseline testing (as in step 2.1), and also have patients undergo another fMRI with a concurrent picture-naming task.

Representative Results

In the site-finding phase of this investigation, most but not all patients respond optimally on the picture-naming task to stimulation of the right pars triangularis[14]. In our experience, patients' performance on picture naming is most consistently facilitated by stimulation of the ventral posterior aspect of the pars triangularis **(Figure 3).**

Long-term improvement in performance on standardized language assessments is illustrated in **Figure 4**. This figure shows results from a representative patient in whom picture-naming accuracy both in the BNT and BDAE (Naming in Categories subsections) increased over time after treatment with rTMS.

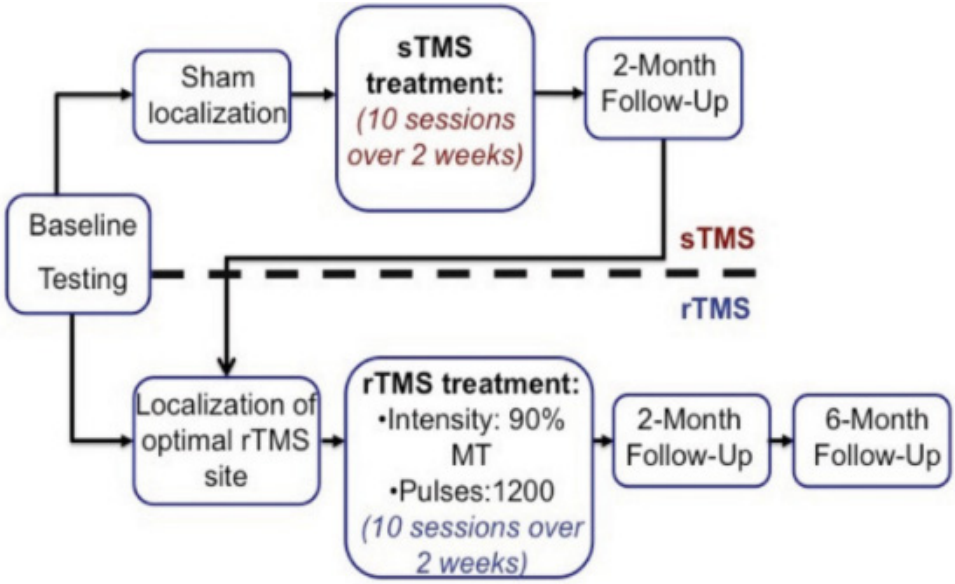

Figure 1. Protocol flowchart. After the two-month visit, all patients in the sham condition cross over to the real rTMS arm.

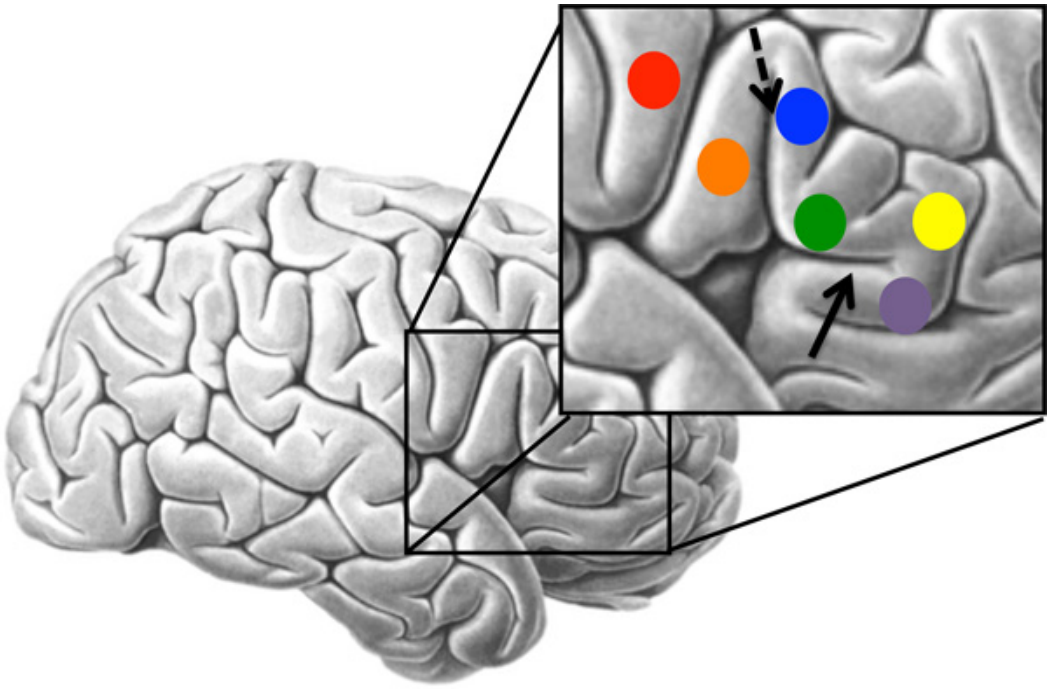

Figure 2. Candidates for Optimal Site of Stimulation. These include M1 corresponding to the mouth (red) and five locations in the rIFG: 1) pars opercularis (BA 44; orange), 2) anterior pars triangularis (BA 45; yellow), 3) dorsal posterior pars triangularis (BA 45; blue), 4) ventral posterior pars triangularis (BA 45; green), and 5) pars orbitalis (BA 47; purple). The solid arrow indicates the anterior horizontal ramus. The hatched arrow indicates the ascending ramus.

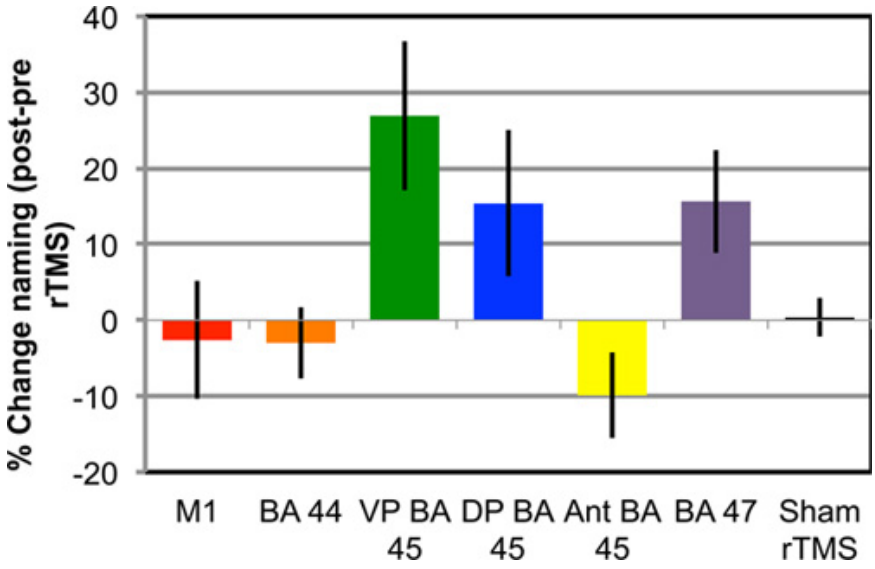

Figure 3. Percent Change in Naming Across Patients. The percent change in performance on a naming task observed before and after rTMS to the six right hemisphere sites during the pre-treatment site-finding phase for nine patients. Vertical lines represent standard error.

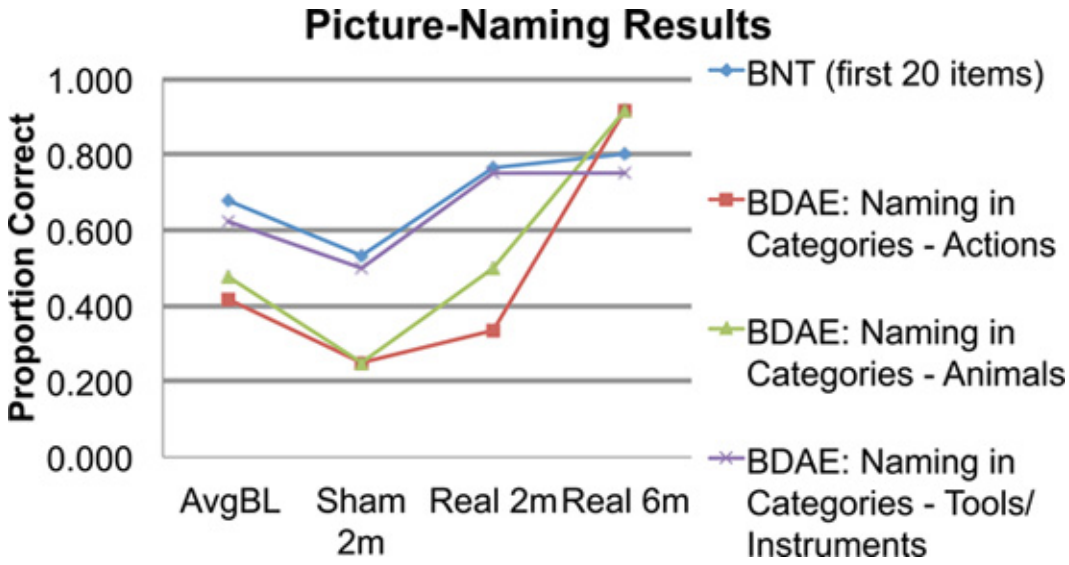

Figure 4. Proportion Correct Over Time in Picture-Naming Tasks for One Patient. Results of the first 20 BNT items and BDAE "Naming in Categories" subsections demonstrate improvement over time.

Discussion

The goal of this article is to detail the steps for identifying a responsive target site in the right hemisphere in patients with chronic non-fluent aphasia. By doing so, we are able to stimulate that target region therapeutically, assess the effects of stimulation on language ability, and use low-frequency rTMS to elicit long-term improvements in naming and fluency in patients with chronic non-fluent aphasia. Our approach replicates and extends methods used by prior investigators, most notably Naeser and colleagues[8]. Importantly, like a number of prior investigators[8,12,13,23], we have observed that most patients undergoing site-finding respond optimally to stimulation of the pars triangularis. However, we have also found that patients vary with respect to optimal site within the pars triangularis, and that a minority exhibit an optimal response to a different site in the right inferior frontal gyrus[11]. This underscores the importance of correct site identification.

One of the limitations of the current approach is that the size of the patient cohorts that are investigated by our studies and by other studies do not lend themselves to quantitative investigation of the relationship between lesion location and response to rTMS at specific sites. A small body of evidence suggests that the distribution of left hemisphere lesions may be an important determinant of response to rTMS in the right pars triangularis. For instance, Martin and colleagues[23] contrasted findings in two aphasic patients who received rTMS to this site, one of whom showed improvement in naming and other language abilities and one of whom did not. The authors hypothesized that differences in the distribution of the patients' lesions may have accounted for differences in response to brain stimulation, emphasizing that the patient who responded poorly to rTMS had a lesion extending beyond the inferior frontal gyrus to encompass dorsal regions of the left motor and premotor cortex, deep white matter near the left supplementary motor area, and the posterior portion of the middle frontal gyrus, a region previously implicated as having an important role in naming ability[24]. Future studies with larger cohorts of patients will allow for additional investigation of the relationship between left hemisphere lesion distribution and the configuration and modifiability of reorganized language networks.

Our current study design has additional potential methodological limitations. For instance, baseline testing is not repeated for patients who initially received sham stimulation prior to receiving real rTMS. While it is conceivable that introduction of sham rTMS and a two-month time interval could result in different baseline level of performance for these patients, there has been no evidence to date to support any change in performance between baseline and 2-month follow-up in patients receiving sTMS. Another methodological limitation is that, owing to the difference in sensory experience between real rTMS and sTMS, it is plausible that some patients receiving sTMS may be aware of the arm of the study to which they have been randomized. However, the design of this experiment is such that that no patient in the sham arm of the study receives real rTMS prior to crossing over into the rTMS arm. We do not, therefore, suspect that patients have clear expectations regarding the sensory experiences associated with TMS. An additional potential methodological limitation of the study is that the picture-naming stimuli used during the site-finding phase may not have controlled for all possible factors. The 40-item lists were matched for frequency, word length, and semantic category. Additionally, the order of the lists was randomized for all subjects. However, certain properties such as age of acquisition and familiarity were not controlled for; this may possibly have impacted the site-finding sessions.

The degree of topographic specificity in the cortex achieved by TMS is somewhat debatable and may be considered a potential study limitation. According to motor mapping studies, the spatial resolution of navigated TMS using a standard 70 mm figure-of-8 coil, is thought to be on the order of 1 cm^2 or less[25]. We thus have reason to believe that TMS is targeting regions as specific as those delineated in this study. Consistent with that notion, our data strongly suggest that the behavioral effects of rTMS differ substantially based on site of stimulation. Furthermore, consistent with the notion that TMS effects in the right inferior frontal gyrus can be highly site-specific, others have published results indicating that rTMS of the right pars triangularis has beneficial effects on picture naming ability in chronic non-fluent aphasics, while stimulation of the adjacent pars opercularis can have deleterious effects[17]. However, it is also important to note that our goal in targeting different regions of the inferior right frontal lobe is not to identify sites in the brain where the effects of TMS are wholly dissociable. Rather, the optimal site-finding phase of the protocol seeks to identify for each subject a target where the effects of TMS seem greatest. Thus, it does not substantively alter the

rationale of the experimental design if the effects of TMS to two nearby regions (*e.g.* dorsal posterior pars triangularis vs. ventral posterior pars triangularis) overlap to some degree.

Recent studies involving transcranial direct current stimulation (tDCS), another form of noninvasive brain stimulation, have demonstrated that patients can experience synergistic gains in language performance when brain stimulation is paired with speech and language therapies[26,27]. Therefore one final potential limitation of our current approach is that none of the subjects included in this protocol were receiving concurrent speech therapy at the time of the study. Future rTMS treatment protocols may be further optimized by pairing stimulation with existing treatments.

Despite these caveats, our emerging data suggest that rTMS may be a promising technique for remediating naming ability, fluency and other language abilities in patients with chronic aphasia. As more investigators explore potential applications of noninvasive brain stimulation in neurorehabilitation and more specifically in aphasia, results like those of the current study are useful, not only because they help to clarify the mechanisms of neural recovery after brain injury but also because they allow for refinement of specific methodological approaches to treatment. For instance, our preliminary finding, based on site-finding procedures, that most patients respond to stimulation of the pars triangularis, may help to establish a more streamlined approach to stimulating individuals with chronic aphasia. Standardization of stimulation approaches may eventually allow for larger clinical trials to be conducted in order to further validate and quantify the efficacy of this and other noninvasive brain stimulation techniques in patients with post-stroke cognitive deficits.

Disclosures

The authors declare that they have no competing financial interests.

Acknowledgements

This work is supported by the following sources of funding:

MAN: NIH 2R01 DC05672-04A2

RHH : NIH/NINDS 1K01NS060995-01A1

RHH: Robert Wood Johnson Foundation/ Harold Amos Medical Faculty Development Program

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