Transcranial Magnetic Stimulation as a Complementary Treatment for Aphasia

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ABSTRACT

Functional brain imaging with nonfluent aphasia patients has shown increased cortical activation (perhaps "overactivation") in right (R) hemisphere language homologues. These areas of overactivation may represent a maladaptive strategy that interferes with, rather than promotes, aphasia recovery. Repetitive transcranial magnetic stimulation (rTMS) is a painless, noninvasive procedure that utilizes magnetic fields to create electric currents in discrete brain areas affecting about a 1-cm square area of cortex. Slow frequency, 1 Hz rTMS reduces cortical excitability. When rTMS is applied to an appropriate cortical region, it may suppress the possible overactivation and thus modulate a distributed neural network for language. We provide information on rTMS and report preliminary results following rTMS application to R Broca's area (posterior, R pars triangularis) in four stroke patients with nonfluent aphasia (5–11 years after left hemisphere stroke). Following 10 rTMS treatments, significant improvement in naming pictures was observed. This form of rTMS may provide a novel, complementary treatment for aphasia.

KEYWORDS: Aphasia treatment, naming, transcranial magnetic stimulation

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Learning Outcomes: As a result of this activity, the participant will be able to: (1) describe some characteristics and background about repetitive transcranial magnetic stimulation (rTMS); (2) describe the rationale for use of this novel technology to help improve speech and naming in stroke patients with aphasia; and (3) describe the type of improvement observed in chronic aphasia patients treated with rTMS, and why it would be appropriate to consider as a complementary treatment for aphasia.

Repetitive transcranial magnetic stimulation (rTMS) has been used in a growing number of research laboratories worldwide since 1985. It is being investigated as a novel intervention to treat disorders such as depression, Parkinson's disease, dystonia (writer's cramp), and epilepsy. Our ongoing research explores whether rTMS can also be applied to help treat stroke patients with aphasia as a complementary treatment to current speech/language therapies.

BACKGROUND OF TMS

TMS is a noninvasive procedure that utilizes magnetic fields to create electric currents in discrete brain areas (for review, see Pascual-Leone and associates[1] and Walsh and Pascual-Leone[2]). TMS involves discharging a current through a coil of copper wire that is held over the subject's scalp. The current pulse flowing through the coil generates a rapidly fluctuating magnetic field that penetrates the scalp and skull unimpeded and induces a changing electrical field in the cerebral cortex below the coil. The physiologic response appears to be caused by current flow in the cortical tissue, which leads to neuronal depolarization (exciting or inhibiting the cortex).[3] The participant feels a "light tap" on the scalp, may feel a twitch of the face muscles, and hears a brief, loud click as the current passing through the coil tightens the copper wire. Participants report that this is not unpleasant. The stimulation of the brain itself is painless.

Multiple stimuli (called "trains") of rTMS of appropriate frequency, intensity, and duration can lead to transient increases or decreases in excitability of the affected cortex that last beyond the duration of the train itself.[4] Slow rTMS (1 Hz), where one magnetic pulse is applied every second, delivered to the motor cortex can give rise to a lasting decrease in corticospinal excitability[5,6] primarily by affecting intracortical facilitation.[7] Applied to other cortical regions, slow rTMS appears to similarly decrease excitability in the targeted cortical region leading to measurable behavioral effects.[8–12] Conversely, fast rTMS (5, 10, or 20 Hz) can induce a transient increase in cortical excitability.[13,14]

The maximum output of a TMS device can be in the range of 1.5 Tesla (e.g., Magstim Rapid Magnetic Stimulator Unit, Magstim Corporation, New York, NY). To achieve focal brain stimulation, TMS is applied with a figure 8-shaped stimulation coil (7 cm in diameter), where the area of cortex affected is $\sim$1 cm square, located at the crossover in the figure 8-shaped coil. See Figure 1.

SAFETY OF rTMS

When higher frequencies are used there is a small risk of undesirable side effects, including seizures. Nevertheless, rTMS appears to be safe if appropriate guidelines are followed.[15,16] Guidelines for the safe use of rTMS were published in 1993[17] and were updated at the First International Workshop on the Safety of Transcranial Magnetic Stimulation held in June of 1996 in Bethesda, MD, USA.[16] These guidelines gave rise to a specific set of precautions and recommendations that have been endorsed by the International Federation of Clinical Neurophysiology.[15,16]

The intensity of the TMS that the participant receives is best adjusted for each TMS session. This can be done by determining the motor threshold, and setting the TMS intensity as a given percentage of the individual's motor threshold at that given time point. Recommendations for safety parameters of rTMS are based on stimulation intensities expressed as a percent of the individual's motor threshold. Motor threshold refers to the intensity of magnetic stimulation needed to elicit a muscle twitch in the thumb in 5 out of 10 trials when using

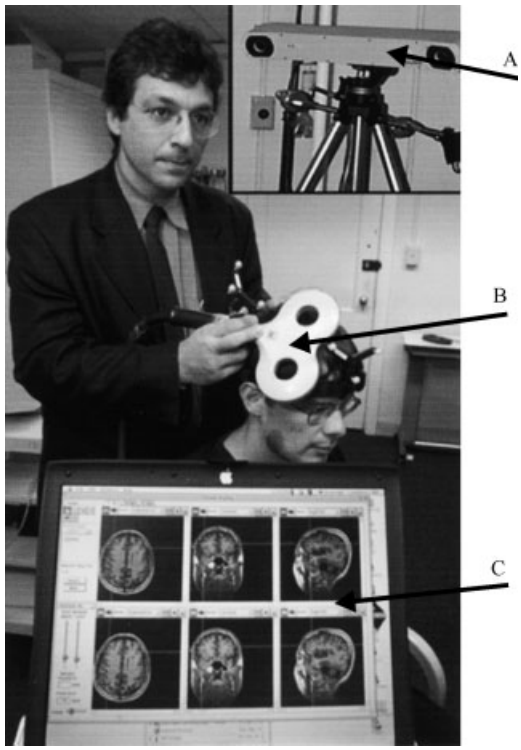

Figure 1 Illustration of the TMS equipment and procedure. (A) Infrared camera used to detect the position of the TMS coil on the participant's head and brain cortex. (B) Figure 8-shaped TMS stimulation coil as it is placed on the scalp to stimulate the brain cortex; it is painless and noninvasive. (C) Structural MRI scan of the participant aids in positioning the TMS coil on the exact region of interest on the brain cortex (Brainsight, Rogue Industries, Montreal, Quebec, Canada). TMS, transcranial magnetic stimulation.

single-pulse TMS applied to the primary motor cortex of the contralateral hemisphere. The motor threshold is reported as a percent of maximum output of the TMS device. There is wide variability in the intensity and duration of TMS stimulation across studies, but these should always follow safety guidelines.

Cortical lesions can change cortical excitability and hence may increase the risk of induction of seizures by exposure to cortical stimulation. TMS (including rTMS) has been used in a large number of studies on stroke patients without complications. Over 1000 stroke patients are reported to have been treated with TMS with no complications.

MODULATION OF CORTICAL EXCITABILITY WITH rTMS

The possibility of modulating cortical excitability with rTMS has generated a large number of trials attempting to apply rTMS for the treatment of a variety of neuropsychiatric conditions. The hypothesis underlying most of these rTMS treatments is that modulation of cortical excitability in cortical areas of dysfunction (as evidenced by functional neuroimaging) may result in clinical benefit for the patients.[4,18]

For example, Siebner and colleagues[19] found that low-frequency rTMS appears capable of normalizing abnormally enhanced motor cortical excitability in some patients with dystonia and has led to symptomatic improvement for hours to days. In their study, the rTMS protocol included a 30-minute train (1800 stimuli) of 1 Hz rTMS at a stimulus intensity of 10% below the motor threshold, administered to the left (L) motor cortex area for the hand in 16 patients with writer's cramp. Some patients (6/16) showed marked improvement in handwriting lasting more than 3 hours. The improvement persisted for several days in two patients. A neurophysiologic study of the effects of the rTMS protocol on cortico-cortical excitability demonstrated that the 1 Hz rTMS protocol reduced intracortical facilitation and enhanced intracortical inhibition. Recently these findings have been confirmed[7,20] and suggest that slow rTMS is capable of reinforcing deficient intracortical inhibition in some patients with dystonia.

EFFECT ON SPEECH IN NORMALS

One of the most dramatic effects of TMS is magnetically induced speech arrest. Several investigators have reported that rTMS over the L frontal cortex can cause subjects to cease speaking, to stutter, or to repeat segments of words. Pascual-Leone and colleagues[21] were the first to induce speech arrest (25 Hz rTMS with a round coil) in a population of epileptic subjects awaiting surgery. The TMS identification of the hemisphere dominant for speech in all six subjects matched that obtained in the sodium amobarbital (Wada) test. The induction of speech arrest by TMS was replicated, in epileptic patients, by Jennum and associates,[22]

using 30 Hz rTMS. They also found a strong concordance with the results of the Wada test. A later study by Epstein and colleagues[23] identified 4 to 8 Hz as the optimum range of rTMS frequency for induction of speech arrest in normal subjects when a specially designed iron-core coil was used. Two recent studies by other investigators[24,25] also obtained speech arrest lateralized to the L hemisphere with frontal stimulation. These studies locate the critical site of stimulation to be over the middle frontal gyrus, dorsal to the inferior frontal gyrus, which is usually referred to as Broca's area. Pascual-Leone and colleagues[21] noted that counting errors and paraphasias could be induced by rTMS to the same sites that led to speech arrest, but at lower stimulation intensities.

Flitman and associates[26] applied rTMS (15 Hz, 750 millisecond trains, 20% above motor threshold) over frontal and parietal lobes while subjects judged whether a word was congruent with a simultaneously presented picture. Subjects were slower to verify the congruency when TMS was applied to the frontal site of the dominant hemisphere. Wassermann and colleagues[27] also showed that rTMS of the dominant hemisphere could disrupt visual naming. Fourteen epilepsy patients were asked to name pictures and words while receiving magnetic stimulation to the motor speech area. Speech arrest was obtained in all but one patient when stimulated over the L hemisphere. In addition, picture naming errors were significantly increased with L hemisphere rTMS while word reading was unaffected.

Picture naming was also examined by Töpper and colleagues,[28] who applied single-pulse TMS over Wernicke's area and motor cortex. TMS over Wernicke's area 500 to 1000 millisecond prior to picture presentation resulted in faster reaction times than control trials. The effect was specific to task and area. These results were replicated in a subsequent study by the same group.[29] Trains of rTMS (20 Hz frequency, 2 second duration) were applied to Wernicke's area while subjects had to name a black-and-white drawing as quickly as possible. Stimulation of L Wernicke's area resulted in significantly shorter reaction times compared with the R hemisphere homologue of Wernicke's area, Broca's area, and primary visual cortex. The authors suggested that rTMS induced a facilitation in lexical search, which resulted in shorter reaction times. These effects raise several questions about why TMS would have facilitatory effects within a system. Factors such as paradoxical lesion effects, that is, disruption of a given area resulting in disinhibition of another remote site, must be considered as well as generalized arousal within the language system.

Stewart and coinvestigators[30] have begun to probe parts of the language system by predicting that Brodmann's area (BA) 37 has a role in phonological retrieval and object naming. They applied rTMS over the posterior region of L and R BA 37 and over the vertex. When rTMS was applied to L BA 37, participants were slower on picture naming but there was no effect on word reading, nonword reading, or color naming. Thus, with respect to object encoding and naming, the posterior region of BA 37 would seem to be critical for recognition.

A recent study by Shapiro and associates[31] used 1 Hz rTMS at 110% of motor threshold to study grammatical distinctions in the frontal cortex and demonstrate the role of the L frontal cortex in representation of verbs as a grammatical class. Selective deficits in producing verbs relative to nouns in speech are well documented in neuropsychology and have been associated with L hemisphere frontal cortical lesions resulting from a variety of causes. This functional-anatomical link, though problematic, has led some researchers to propose that verb retrieval is mediated by L frontal or frontostriatal circuits that also subserve motor planning. These investigators used rTMS to target a portion of prefrontal cortex along the middle frontal gyrus anterior and superior to Broca's area while subjects performed a linguistic task involving regular nouns or verbs. Average response time for verbs *increased* following rTMS, a change that was both qualitatively and quantitatively different from that seen after the noun condition or the sham stimulation. This suggests that verb production had been specifically hindered. These results demonstrate for the first time that neural circuits in the L frontal cortex adjacent to Broca's area are critical at some stage in the spoken production

of verbs by unimpaired individuals. This and the other studies mentioned illustrate the potential of TMS in studies of linguistic processing.

SIGNIFICANCE OF PREVIOUS STRUCTURAL AND FUNCTIONAL IMAGING STUDIES IN APHASIA

Structural imaging studies have begun to clarify the issue of potential for recovery of speech in nonfluent aphasia patients. For example, Naeser and colleagues[32,33] employed structural imaging (CT and MRI) with nonfluent aphasia patients and delineated a specific L hemisphere lesion site pattern in subcortical white matter, which is associated with mild-moderate nonfluent speech, and a more extensive white matter lesion pattern associated with severe nonfluent speech.

Functional imaging studies with chronic aphasia patients have also begun to examine levels of cortical activation during language-related tasks. Some functional imaging studies have observed activation in remaining L hemisphere cortical regions of interest (ROIs) to have a primary role in aphasia recovery.[34–39] Other studies have observed activation in nondamaged R hemisphere ROIs to have a primary role.[40–44] Each hemisphere may be important, depending on the type of language behavior and when it was examined.[40,45–50]

Recent functional magnetic resonance imaging (fMRI) research with chronic nonfluent aphasia patients has indicated that these patients appear to have excess blood flow in certain areas of the brain while producing nonfluent speech. Naeser and colleagues[51] used the Dynamic Susceptibility Contrast fMRI method to study overt propositional speech in chronic nonfluent aphasia patients. While producing normal speech, controls had significantly higher relative cerebral blood volume (relCBV) in the L supplementary motor area (SMA) than in the R SMA. In contrast, while producing nonfluent speech, the aphasia patients had significantly higher relCBV in the R SMA than in the L SMA. Additionally, the patients had significantly higher relCBV in the R sensorimotor mouth during nonfluent speech (versus a nonverbal control condition). This R sensorimotor mouth relCBV in the patients was also significantly higher versus the controls during speech.

Although functional imaging studies are beginning to show the cortical regions activated during language tasks in stroke patients with aphasia, the effect of activation in these regions is still largely unknown. Also unknown is whether the R hemisphere activation observed in nonfluent aphasia patients is beneficial or maladaptive. This activation or overactivation observed in nonfluent patients may represent a dead-end or maladaptive strategy rather than a beneficial one[40,43] and it may limit, rather than account for, aphasia recovery in nonfluent patients.

The results from the above-mentioned studies suggest that poor modulation, including possible overactivation of R perisylvian language homologues, may in part underlie the hesitant, poorly articulated, agrammatic speech associated with chronic nonfluent aphasia patients. If so, suppression of this overactivation may result in improved speech and language behavior.

CONCEPT FOR rTMS TREATMENT

While it may seem paradoxical to suggest that promoting inhibition in R hemisphere ROIs would promote improved naming ability or speech, there are animal studies and some human case reports which suggest that direct or indirect neural "damage" to specific areas in the central nervous system may result in facilitation of behavior (see Kapur[52] for review). Kapur has labeled this phenomenon as "paradoxical functional facilitation" (PFF). PFF is known as the "Sprague effect" in animal studies where, for example, a new lesion in the superior colliculus was observed to improve visual functioning and visual attention following an initial occipito-parietal lesion in cats. In humans, there are case studies whereby ambidextrous adults who had stuttered since childhood stopped stuttering following focal brain damage in adulthood (e.g., stroke or head injury), even as soon as 10 days postonset.[53] Vuilleumier and colleagues[54] reported the disappearance of L-sided unilateral neglect, brought on by a R parietal infarct, after the occurrence of a second lesion in the area of the L frontal eye field.

Disruption of a given element in a neural network using rTMS may promote improved task performance by modulating activity in remote, trans-synaptically affected neural structures. This parallels the notion of PFF.[52]

RESEARCH WITH rTMS TO IMPROVE NAMING IN APHASIA

The ability to name pictures was chosen as a measure of language behavior because it has been observed that there is continued improvement for 5 to 10 years poststroke in some aphasia patients.[55] Based on our current understanding of overactivation in R hemisphere language homologues in nonfluent aphasia patients during speech, we are developing a new language rehabilitation treatment approach for these patients using rTMS. There are two phases to our rTMS research.

Phase 1 rTMS Treatments

In Phase 1, we apply slow 1 Hz rTMS for 10 minutes (90% of motor threshold) to at least four different R perisylvian language homologues, during different rTMS sessions.[56] Phase 1 sessions determine which single ROI might produce the Best Response (most improvement in naming pictures) for an individual nonfluent patient. The patient's ability to name pictures is immediately tested after the 10-minute rTMS treatment, with a list of 20 Snodgrass and Vanderwart[57] pictures. There are five 20-item lists. Each list has the same level of difficulty/complexity. The internal order is randomized and the list presentations are randomized. After rTMS treatment to a specific ROI, if the patient's ability to name pictures is at least 2 SD above baseline testing, then that ROI is considered to be the Best Response ROI for that individual patient.

To date we have studied six chronic stroke patients (four male and two female; age range 51–67 years; 1–30 years post L hemisphere stroke). Five had nonfluent speech that ranged in severity from mild to severe. One had recovered from a nonfluent Broca's aphasia to anomic aphasia. We applied slow 1 Hz rTMS to transiently suppress activity in R hemisphere language homologues as identified by MRI-guided frameless stereotaxy (see Fig. 1). We evaluated the effects on picture naming from focal disruption of R pars triangularis (BA 45); R pars opercularis (BA 44); R posterior superior temporal gyrus (BA 22); and R motor cortex (M1) mouth area (orbicularis oris).

All six patients correctly named the highest number of pictures following application of rTMS to the posterior gyral portion of the pars triangularis part of R Broca's homologue (R BA 45). In five of the six subjects this improvement was statistically significant as compared with the individual baseline performance and it was the Best Response ROI. Overall, there was a significant effect of site of rTMS stimulation on both number of pictures named correctly (repeated measures ANOVA F-value 8.3; $p = 0.001$) and response time (repeated measures ANOVA F-value 3.6; $p < 0.05$). Patients named significantly more items after rTMS to R BA 45 than to R BA 44 ($p < 0.0005$), R M1 ($p < 0.005$), and R BA 22 ($p < 0.001$). On average this resulted in three more items named correctly after rTMS to R BA 45 than at baseline or after any of the other ROIs stimulated with rTMS. Following rTMS to R BA 44, all subjects tended to name fewer items and were significantly slowed in their reaction times (versus R BA 22, $p < 0.05$; versus R BA 45, $p < 0.01$; and versus R M1, $p < 0.01$). It is assumed that the 10 minutes of 1 Hz rTMS suppressed excitation in R BA 45 which in turn resulted in improved modulation, at least in part, of R perisylvian homologues and the bi-hemispheric network associated with naming, leading to improved naming ability. Thus, while the abnormally high, increased R perisylvian activation during nonfluent speech has been suggested to be maladaptive, perhaps some modulated activation may be beneficial.

Phase 2 rTMS Treatments

In Phase 2, we apply slow 1 Hz rTMS for 20 minutes, 5 days a week for 2 weeks (90% of motor threshold) to the Best Response ROI for an individual patient based on results from the Phase 1 rTMS sessions. In Phase 2 we treated four R-handed, chronic aphasia patients (age range, 52–58 years; 5–11 years poststroke),

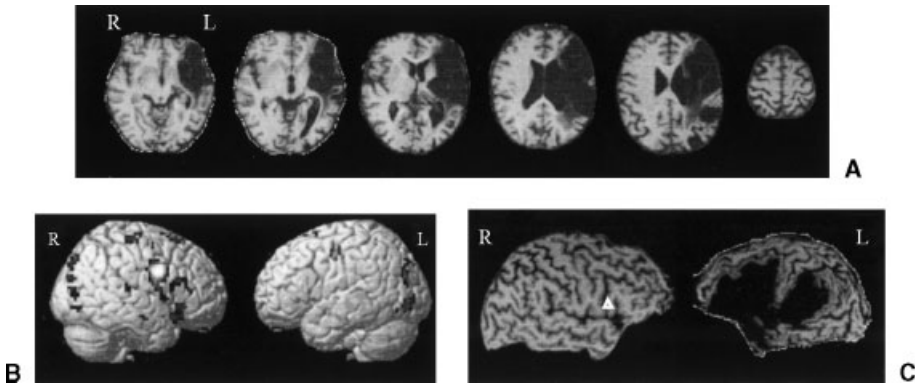

Figure 2 Structural and functional MRI for a mild nonfluent aphasia patient (58-year-old male, 9.5 years poststroke) before rTMS treatment. (A) Structural (axial) MRI scan. (B) Functional MRI scan during overt picture naming before Phase 2 treatment with rTMS. Note the increased activation in right hemisphere perisylvian language regions, especially motor cortex (mouth) and Broca's area (pars triangularis, right BA 45). (C) Left and right lateral views of this patient's brain reconstructed from structural MRI. The triangle marks the posterior gyral portion of right BA 45 (pars triangularis, part of right Broca's area) which was stimulated with the magnetic coil during each 20-minute rTMS treatment session of Phase 2. rTMS, repetitive transcranial magnetic stimulation; BA, Brodmann's area.

who were recovered Broca's/anomic, mild nonfluent, moderate nonfluent, or severe nonfluent patients.[58] The Best Response ROI from Phase 1 for each patient was the posterior gyral portion of R BA 45. On language testing performed at 2 months post-rTMS, each patient improved in naming on standardized tests. For example, there was significant improvement on the first 20 items of the Boston Naming Test,[59] ($t = -8.66$, $p = 0.003$) with an average increase of 42%. There was also significant improvement on specific naming subtests of the Boston Diagnostic Aphasia Exam,[60] including the 12 tools/implements ($t = -3.67$, $p = 0.035$) with an average increase of 96%; and the 12 animals ($t = -5.0$, $p = 0.015$) with an average increase of 49%.

Future fMRI research may show which specific ROIs in an aphasia patient have overactivation to help guide rTMS treatment for that patient. Figure 2 shows an fMRI scan during overt naming, for a 58-year-old man with mild nonfluent aphasia before Phase 2 rTMS treatments.[61] This fMRI scan shows overactivation for this task, primarily in R-hemisphere language homologues. He benefited from application of the slow 1 Hz rTMS to R BA 45 in Phase 2. See graphs in Figure 3.

One of our patients with severe nonfluent speech has had follow-up testing for 8 months

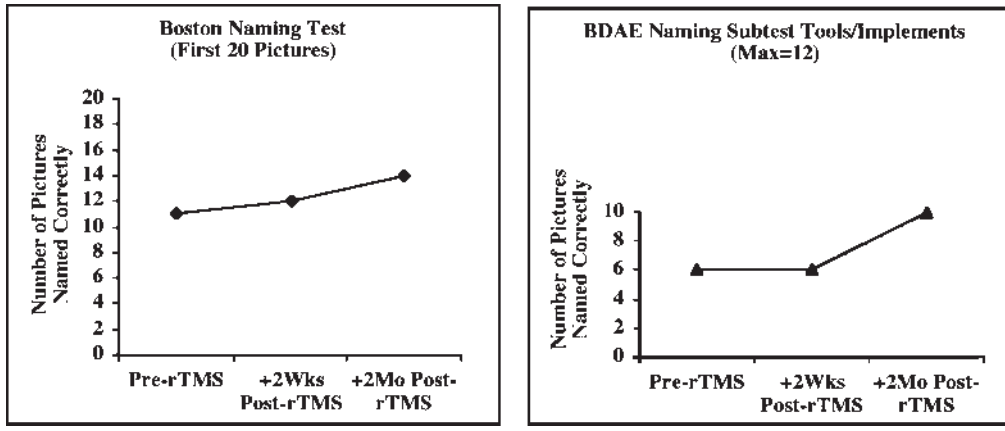

Figure 3 Naming data acquired before and after 2 weeks of rTMS treatments for patient shown in Figure 2.

after the last rTMS treatment in Phase 2.[62] She is a 56-year-old woman who was 6 years post L intracerebral hemorrhage (subcortical lesion only). On pre-rTMS testing, she earned a score of 4 on the first 20 items of the Boston Naming Test; at 2 months post-Phase 2 rTMS her score was 7; and at 8 months her score was 12. On the Boston Diagnostic Aphasia Exam naming subtests, there was also improvement in her ability to name tools/implements. Pre-rTMS, her score was 2; at 2 months post-Phase 2 rTMS, her score was 3; and at 8 months it was 5. Her pre-rTMS score on the Boston Diagnostic Aphasia Exam subtest for naming animals was 0; at 2 months post-Phase 2 rTMS her score was 1; and at 8 months it was 6.

This patient received no speech therapy between rTMS and subsequent retesting. If the brain is undergoing reorganization during 2 to 8 months post-rTMS, this may be an ideal time to provide speech therapy. A combination approach to treatment (rTMS followed by a period of speech therapy) may promote better recovery.

It is posited that 1 Hz rTMS decreased excitation in R BA 45, which in turn modulated activity in the distributed, bi-hemispheric language network and this led to improved naming. This network may include occipital regions BA 17, 18, 19[63,64] and temporal regions BA 37, 22, 21, or 20.[65–69] Further investigation with functional imaging is needed to verify the regions that comprise this network.

rTMS TREATMENT AND MOOD STATE

We observed no negative side effects or complications during or after the rTMS treatment sessions. Patients report subjectively that it is easier for them to recall words and name pictures. Klein and colleagues[70] reported a significant antidepressant effect of 1 Hz rTMS applied to R prefrontal cortex in patients with treatment-resistant major depression. Therefore, we have begun to investigate possible mood effects of R frontal rTMS treatment in our aphasia patients. To date, we have studied three R-handed males with chronic aphasia (age range, 52–58 years; 5–11 years poststroke) who had recovered Broca's/anomic aphasia or mild-moderate nonfluent aphasia. Data were collected pre-Phase 2 rTMS treatment, at 2 weeks and at 2 months post-rTMS treatments using a Visual Analog Scale for rating mood.[71] A one-way repeated measures ANOVA showed a significant increase (F-value 11.76; $p = 0.02$) in the "happiness" score post-rTMS and the "sadness" score decreased in two out of three (the third patient indicated little "sadness" pre-rTMS and therefore had little room for change, i.e., decrease in sadness score). These mood effects may be secondary to the improvement in naming ability, but there may be rTMS-induced mood effects from R frontal stimulation independent of language effects.[72]

These data are considered preliminary. The patients' reports of improvement in mood, their increased ease in the ability to recall words, and even task performance may be driven by patient expectations. A randomized, controlled trial using sham treatments to determine how much of a role subject expectation may have, will be an important consideration for the future application of rTMS as a complementary treatment for aphasia.

CONCLUSION

rTMS allows noninvasive stimulation of the human cortex. It is an innovative new tool in the study of the neurobiology of language in humans. Slow 1 Hz rTMS can give rise to a lasting decrease in cortical excitability. Using the notion of PFF, one may be able to utilize 1 Hz rTMS to suppress activation in a specific ROI that has been observed to have high blood flow (presumed overactivation) on fMRI. Suppression of that specific ROI may have an overall modulating effect on the remaining neural networks for language.

Although it is unknown whether long-term recovery in naming ability is related to brain reorganization in both hemispheres, a possible role for the R hemisphere has been suggested for some patients.[73] Our preliminary research shows that rTMS applied to the posterior, gyral portion of R BA 45 (part of R Broca's area) improves naming in chronic, nonfluent aphasia patients. When applied to the appropriate cortical region, rTMS may provide

a complementary treatment approach for aphasia.[56] When combined with current speech and language therapies for aphasia, rTMS may help to promote better recovery of language.

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