SPECIAL COMMUNICATION

Transcranial Magnetic Stimulation and Aphasia Rehabilitation

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Repetitive transcranial magnetic stimulation (rTMS) has been reported to improve naming in chronic stroke patients with nonfluent aphasia since 2005. In part 1, we review the rationale for applying slow, 1-Hz, rTMS to the undamaged right hemisphere in chronic nonfluent aphasia patients after a left hemisphere stroke; and we present a transcranial magnetic stimulation (TMS) protocol used with these patients that is associated with long-term, improved naming post-TMS. In part 2, we present results from a case study with chronic nonfluent aphasia where TMS treatments were followed immediately by speech therapy (constraint-induced language therapy). In part 3, some possible mechanisms associated with improvement after a series of TMS treatments in stroke patients with aphasia are discussed.

Key Words: Aphasia; Rehabilitation; Stroke; Transcranial magnetic stimulation.

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REPETITIVE TRANSCRANIAL magnetic brain stimulation has been studied worldwide since 1985[1] as a potential treatment for some disorders associated with stroke, including paralysis or hemispatial visual neglect, as well as to treat other disorders such as depression and epilepsy.[2] This article presents an overview of repetitive transcranial magnetic stimulation (rTMS) where this new technology is explained in relationship to treatment of aphasia. In part 1, we present the rationale for using rTMS on the right hemisphere (RH) in chronic nonfluent aphasia patients with left hemisphere (LH) stroke. We also present a transcranial magnetic stimulation (TMS) protocol associated with long-term, improved naming post-TMS treat-ment, and review a related functional magnetic resonance (fMRI) study. In part 2, we briefly review a case study where TMS was combined with constraint-induced language therapy (CILT). In part 3, we conclude with a review of possible mechanisms underlying language improvement post-TMS.

TMS is a noninvasive procedure that uses magnetic fields to create electric currents in discrete brain areas.[3,4] 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.[5] 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.

When rTMS is applied as multiple stimuli (trains) of appropriate frequency, intensity, and duration, rTMS can lead to increases or decreases in excitability of the affected cortex that last beyond the duration of the train itself.[6] Slow rTMS, where 1 magnetic pulse is applied every second (1Hz), delivered to the motor cortex can give rise to a lasting decrease in corticospinal excitability.[7,8] Conversely, fast rTMS (5, 10, or 20Hz) can induce a transient increase in cortical excitability.[9] The maximum output of a TMS device can reach up to 2.5T. To achieve focal brain stimulation, rTMS is often applied with a figure 8-shaped stimulation coil (7cm in diameter), where the area of the brain cortex affected is approximately 1cm³, located in the center where the 2 wings of the figure 8-shaped coil meet.

List of Abbreviations

AF	arcuate fasciculus
BA	Brodmann's area
BDAE	Boston Diagnostic Aphasia Exam
BNT	Boston Naming Test
CILT	constraint-induced language therapy
FDI	first dorsal interosseus muscle
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
LH	left hemisphere
MT	motor threshold
POp	pars opercularis
PTr	pars triangularis
RH	right hemisphere
ROI	region of interest
RT	response time
rTMS	repetitive transcranial magnetic stimulation
SLP	speech-language pathologist
SMA	supplementary motor area
SMG	supramarginal gyrus
TMS	transcranial magnetic stimulation
vPMC	ventral premotor cortex

PART 1: RATIONALE FOR TMS, AND A TMS TREATMENT PROTOCOL FOR APHASIA

Rationale

Functional imaging studies of language in patients with nonfluent aphasia frequently reveal an increased activation (possible overactivation) in RH language homologues.[10-14] It is possible that unusually high activation in the RH is related to transcallosal disinhibition leading only to partial, or incomplete, recovery. Such increased RH activation would represent maladaptive plasticity, and lead to a dead-end, inefficient strategy for recovery.[2,10,12,14,15]

Several studies have suggested that for long-term recovery, RH recruitment may be less efficient than restoring the LH network. Patients with better recovery have been observed to have higher activation in left superior temporal gyrus and left supplementary motor area (SMA).[16-18] A study using perfusion-weighted imaging in acute stroke patients has shown improved naming to be associated with reperfusion of left Brodmann's area (BA) 37.[19] As early as 2 weeks poststroke onset, better performance on a verbal fluency test (and better recovery) was found to be associated with activation of the left inferior frontal gyrus (IFG).[20]

After speech-language therapy in some chronic stroke patients, new LH activation has been associated with improved language.[21-24] However, in some studies, new RH activation has also been observed after speech-language therapy.[25-28] RH participation in the acute recovery stage of LH stroke may be followed later, by LH activation corresponding to further recovery; the RH may play a larger role in supporting recovery when there is greater damage to LH language areas.[29] It thus remains unclear whether recovery in aphasia is mediated primarily from LH undamaged language or perilesional regions, or from RH language homologues, or from both. It is possible that different mechanisms may be engaged by different individuals. Regardless, there seems to be potential for brain reorganization and improved language, even in chronic, poststroke aphasia.[15,30-32]

Naeser et al[33] have hypothesized that suppression of a cortical region of interest (ROI) in the RH, with 1-Hz rTMS could result in a decrease of overactivation in that ROI, and in some patients, lead to an overall modulation of the bilateral neural network for naming. This may include reactivation of some areas within the damaged LH, and ultimately a functional language improvement. This notion is consistent with the phenomenon of Paradoxical Functional Facilitation[34] that suggests direct or indirect neural damage or disruption of a specific area in the central nervous system may result in facilitation of behavior across functional neural networks.[35]

TMS Treatment Protocol With Nonfluent Aphasia Patients

The studies by Naeser et al,[33,36,37] have included chronic aphasia patients who are at least 6 months postsingle, unilateral LH stroke. They were right handed, native English speakers, and ranging in age from 40 to 73 years (allowing ≤age 80). If there was a history of seizures, they were well controlled with medication, and the patient had not had a seizure for at least 1 year prior to entry. Slow, 1Hz rTMS, however, has been used to help treat seizures.[38] Patients had nonfluent speech, with a 1 to 4 word phrase length as measured with elicited propositional speech on the Cookie Theft Picture, Boston Diagnostic Aphasia Exam (BDAE).[39,40] Patients named at least 3 pictures out of 60 on the Boston Naming Test (BNT),[41] but not more than 47 (to allow for potential improvement). The primary language

outcome measures were the BNT and naming subtests on the BDAE.

In addition, prior to any rTMS sessions, a baseline naming ability for Snodgrass & Vanderwart[42] pictures was established. During the baseline Snodgrass & Vanderwart naming testing, ten, 20-item Snodgrass & Vanderwart picture lists were administered. Across the 10 Snodgrass & Vanderwart lists, the baseline mean number of Snodgrass & Vanderwart pictures named correctly was calculated, as well as the baseline mean response time (RT).

Phase 1 TMS: locate the best-response RH ROI to suppress with TMS. During Phase 1 of TMS in the studies by Naeser et al,[43] the best-response RH cortical ROI was located for each patient. This ROI was defined as that ROI, which when targeted with 1Hz rTMS for 10 minutes, resulted in an immediate significant improvement in naming, as compared with baseline naming. (This improvement in naming is only temporary, during the Phase 1 TMS protocol.) This ROI later becomes the targeted location for rTMS during Phase 2 TMS (20min of rTMS for 10d), for that patient.

In the protocol of Naeser,[43] during Phase 1 TMS, the effect of slow, 1-Hz rTMS for 10 minutes was used to suppress activity in each of at least 4 different RH frontal ROIs in separate TMS sessions. A total of 600 magnetic pulses at 90% of motor threshold (MT) for the left first dorsal interosseus muscle (FDI) was delivered to each RH ROI using the Super-Rapid High Frequency Magnetic Stimulator.[a] Published guidelines for safety parameters of rTMS are based on stimulation intensities expressed as a percent of the individual's MT.[44-46] A figure-8 shaped rTMS coil with a 7-cm outside diameter on each wing was used. The RH cortical ROIs that were examined included the right primary motor cortex representation for the mouth (orbicularis oris muscle, as verified with motor evoked potentials), and at least 3 subregions within right Broca's area homologue, as described below. These subregions were labeled according to sulcal and gyral boundaries[36,47,48] (fig 1).

The vertical ascending ramus is traditionally the most common sulcus used to separate the pars opercularis (POp) from the pars triangularis (PTr) within Broca's area. However, in some cases, a diagonal sulcus is present. Cytoarchitectonic studies have observed, for example, that a diagonal sulcus was present in every second hemisphere, and it can either mark the border between BA 44 (likely POp) and BA 45 (likely PTr), or be located inside BA 44.[47] Thus, when a diagonal sulcus is present, without cytoarchitectonics, it is not possible to know whether the diagonal sulcus is actually a border between POp and PTr, or if it is within POp. Taking this into consideration, when a diagonal sulcus is present in an aphasia patient who is participating in TMS treatment, it is important to carefully examine at least 4 subregions within right Broca's homologue, as shown in figure 1.[36]

The exact location of the best response RH ROI to suppress with 1Hz rTMS can vary somewhat, from patient to patient, and the ROI needs to be firmly established for each case. Suppression of POp often impairs naming and/or increases RT.[43] The best response area is often reported to be located immediately anterior to the POp, for example, the right posterior PTr.[33,36,37,49,50]

A frameless stereotaxic system[b] is used in combination with the patient's 3-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) magnetic resonance imaging (MRI) scan, in order to guide the rTMS coil placement onto the targeted ROI. After each 10-minute rTMS application to a specific RH ROI during Phase 1, a 20-item Snodgrass & Vanderwart set of pictures is presented for the patient to name. A best response RH ROI is defined as that ROI which is
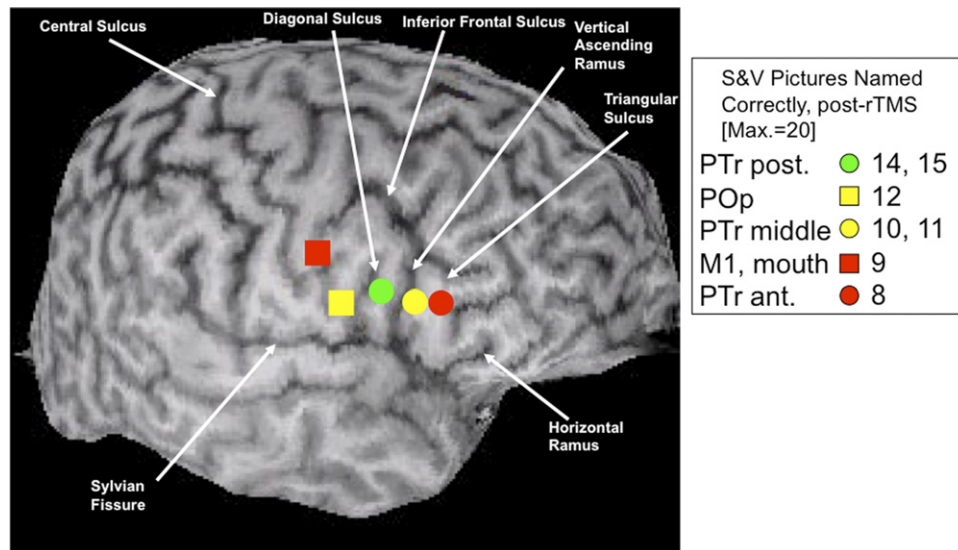
Fig. 1. Legend box shows naming data for a single aphasia case acquired immediately after suppression of 5 different RH cortical ROIs during exploratory Phase 1 TMS. Location of 5 frontal, RH ROIs are shown where each was suppressed in separate TMS sessions, with 1-Hz rTMS for 10 minutes. These 5 ROIs included right M1, mouth (orbicularis oris muscle, as verified with motor evoked potentials), and 4 subregions within right Broca's area as defined in the text, using sulcal boundaries (arrows). A diagonal sulcus was present in the RH in this case. The PTr posterior ROI (green symbol) was the best-response ROI, that is, the area associated with a naming score that reached at least 2 SD above baseline Snodgrass & Vanderwart naming ability (eg, 15). During Phase 2 TMS, the PTr posterior ROI (green symbol) was used as the target for suppression with 1-Hz rTMS for ten, 20-minute treatments in this case. Note that the number of pictures named correctly immediately post-rTMS decreased for any given ROI, as the distance from the best-response ROI increased by 1 or 2cm in an anterior or posterior direction. Abbreviation: S&V, Snodgrass and Vanderwart. From Naeser MA, Martin PI, Lundgren K, et al. Improved language in a chronic nonfluent aphasia patient after treatment with CPAP and TMS. Cogn Behav Neurol 2010;23:29-38. Reprinted with permission from Wolters Kluwer Health and authors' permission.[36]

associated with a Snodgrass & Vanderwart naming score that is at least 2 SD above the baseline mean number of Snodgrass & Vanderwart pictures named correctly.

Phase 2 TMS: 2-week treatment to suppress the best-response RH ROI with TMS. In the studies by Naeser et al[33,36,37,49] during Phase 2, the best-response RH ROI from Phase 1 is targeted for 20 minutes of rTMS, once a day, 5 days a week, for 2 weeks. On each day of treatment, the rTMS is applied at 1Hz frequency (1200 pulses) at 90% of MT (left FDI), using the same magnetic stimulator device as in Phase 1. The frameless stereotaxic system is again used to guide the location of the rTMS coil on the patient's scalp. Online monitoring allows documentation of accurate targeting of the best response RH ROI throughout the TMS session, and from day-to-day. Coil orientation is held constant across sessions, at

approximately 45°. No side effects or complications have been reported with these parameters.[45,46] In order to test for possible long-term effects post-TMS, language testing is completed at 2 months and at 6 months post-Phase 2 TMS.

Results, Language Outcome Measures Post-Phase 2 TMS

Naeser et al[33] have reported at 2 months post-10 rTMS treatments to suppress the right PTr; significant improvement on 3 naming tests was observed: (1) the first 20 items of the BNT ($P=.003$); (2) the BDAE Animals subtest ($P=.02$); and (3) the BDAE Tools/Implements subtest ($P=.04$) in 4 chronic nonfluent aphasia patients. At 8 months post-TMS, all 3 naming test scores continued to improve relative to pre-TMS testing, but only Tools/Implements was still significant ($P=.003$). BNT and naming Animals failed to reach significance because

Table 1: Language Testing for Mild Nonfluent Aphasia Patient, Pre- and Post-TMS[36]

Language Tests	Pre-TMS Baseline	3-mo Post-TMS	6-mo Post-TMS	2.4-y Post-TMS
BNT	(3 sessions) 8.67±1.41[†]	12*	13*	(3 sessions) 14.33*±1.15[†]
Longest maximum phrase length (Cookie Theft picture description, BDAE)	5	11	7	12

Speech Samples for Longest Phrase Length		
3-mo Post-TMS	6-mo Post-TMS	2.4-y Post-TMS
"His mother wash the dish up and the water fall down."	"His mother was watching the paper plates."	"She was getting her cookie jars and she started to fall back."

*$P<.05$.
[†]Mean ± 2 SD.

Table 2: Language Testing for Mild-Moderate Nonfluent Patient, Pre- and Post-TMS50

Language Tests	Pre-rTMS Baseline	2-mo Post-rTMS	6-mo Post-rTMS	16-mo Post-rTMS	43-mo Post-rTMS
Language Testing for Patient 1, Mild-Moderate Nonfluent Aphasia Patient (good response), Pre- and Post-TMS[50]					
BNT	11	14	18	15	15
Longest maximum phrase length (Cookie Theft picture description, BDAE)	3	5	5	5	6

Language Tests	Pre-rTMS Baseline	2-mo Post-rTMS	6-mo Post-rTMS
Language Testing for Patient 2, Severe Nonfluent Aphasia Patient (no response), Pre- and Post-TMS[50]			
BNT	(3 sessions) 1.67 ± 1.15[†]	1	1
Longest maximum phrase length (Cookie Theft picture description, BDAE)	1	1	1
Auditory comprehension commands, BDAE	8.67 ± 1.15[†]	11*	11*
Auditory comprehension complex ideational material, BDAE	2.33 ± 0.58[†]	2	4*

*$P<.05$.
[†]Mean $\pm$ 2 SD.

of 1 of the 4 patients. Improvement was also observed in number of words per longest phrase length in elicited, propositional speech (BDAE) for 2 of the patients at 2-months post-TMS. A mild nonfluent patient increased from a 3-word phrase length to a 5-word phrase length (Cookie Theft picture, BDAE); and a moderate nonfluent patient increased from a 1-word phrase length to a 3-word phrase length.

Similar positive results have been observed with another mild nonfluent aphasia patient who started TMS treatments at 2.4-years poststroke.[36] After determination of this patient's best response RH ROI to suppress from Phase 1 TMS (see Phase 1 TMS results for this case) (see fig 1), the patient entered and completed Phase 2. At 3- and 6-months post-Phase 2 TMS treatments, this patient's BNT scores improved significantly (>2 SD) from baseline (table 1). At 27-months post-TMS (4.6-y poststroke), his increase on the BNT remained significant compared with baseline. An improvement in the longest phrase length (Cookie Theft picture, BDAE) was also observed in this patient, post-TMS. See table 1 for language data and speech samples for his spontaneous speech pre- and post-Phase 2 TMS. He received no individual speech therapy during or post-TMS. Another chronic nonfluent aphasia patient treated at 7-years poststroke using the same TMS protocol also showed increased phrase length and complexity in elicited, propositional speech at 2-, 6-, and 10-months post-TMS.[49]

fMRI, Pre- and Post-TMS

fMRI has been used to examine brain activation during overt naming, pre- and post- a 2-week TMS treatment series (Phase 2 TMS) in 2 chronic nonfluent aphasia patients.[50] One patient (Patient 1) improved in naming and phrase length in propositional speech, lasting at least 2-years post-TMS. The other patient (Patient 2) showed no change in naming or propositional speech post-TMS.

For Patient 1, language was tested at 2-, 6-, 16-, and 43-months post-Phase 2 TMS. He had significant improvement on the BNT and the longest phrase length (Cookie Theft picture, BDAE). Auditory comprehension was largely unchanged (table 2).

For Patient 2, pre-TMS language testing was performed at baseline (1.5-y poststroke), and at 2- and 6-months post-Phase 2 TMS. His spontaneous speech consisted primarily of only stereotypies. He had no change on the BNT or in the longest phrase length (Cookie Theft picture, BDAE). He improved by 2 SD post-TMS on BDAE Auditory comprehension subtests for Commands at 2 and 6 months post-TMS and Complex Ideational Material at 6 months (see table 2).

Results from this overt naming fMRI study by Martin et al,[50] showed that at pre-TMS (as well as at 3-mo and at 16-mo post-TMS), Patient 1 had activation in the right and left sensorimotor cortex (mouth area), the right IFG, and in the right and left SMA. At 16-months post-TMS, however, there was a significant increase in activation in the left SMA, compared with pre-, and to 3-months post-TMS ($P<.02$; $P<.05$, respectively). There was also a trend toward significantly greater activation in left SMA than right SMA at 16-months and 46-months post-TMS ($P<.08$; $P<.09$, respectively). Pre-TMS there had been no difference between left and right SMA activation. A shift to stronger left SMA activation was first observed at 16-months post-TMS. At this time, his highest accuracy rate for picture naming (58%) was observed, compared with only 28% pre-TMS and 42% at 3-months post-TMS. There were no intervening overt speech fMRI scans between 3 and 16 months post-TMS. The new LH activation remained present, even at 46-months post-TMS (nearly 4y post-TMS), when the patient was almost 14-years poststroke.

Results from overt naming fMRI with Patient 2 showed that pre-TMS significant activation in the right IFG was present and he named only 3% of the pictures. At 3- and 6-months post-TMS, there was no longer significant activation in the right IFG (the area suppressed with 1-Hz rTMS), but significant activation was present in the right sensorimotor cortex. Although Patient 2 had significant activation in both the left and right SMA on all 3 fMRI scans (pre-TMS, and at 3- and 6-mo post-TMS), ROI analyses showed no difference across sessions in the left or right SMA activation.[50] In addition, suppression of right PTr with rTMS resulted in no new, lasting perilesional LH activation across sessions. His naming remained only at 1 to 2 pictures during all 3 fMRI scans. His BNT score and longest phrase length remained at 1 word post-TMS.

Lesion site likely played a role in each patient's fMRI activation pattern, and level of response to TMS treatment. Patient 2 had an atypical frontal lesion in the left motor and premotor cortex that extended high, near the brain vertex, with deep white matter lesion near left SMA. Additionally, Patient 2 had lesion in the posterior middle frontal gyrus at the junction of the premotor cortex, an area important for naming.[51] Patient
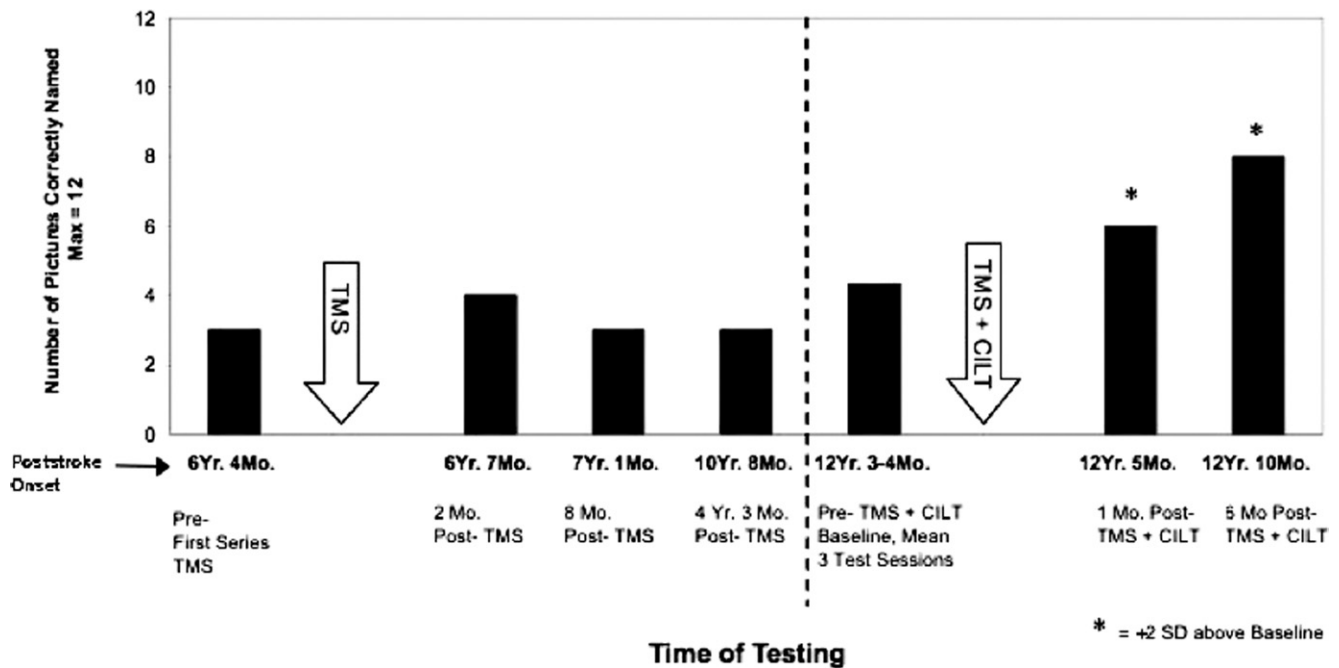
Fig 2. Language Outcome Measure: BDAE Action Naming. Significant improvement in Action Naming test scores postintervention (TMS and CILT) for a severe nonfluent global aphasia patient. The bar graph shows significant improvement (>2 SD) in BDAE verb Action Naming at 1- and 6-months post-TMS plus CILT compared with baseline testing preintervention. The bar graph also displays previous scores, pre- and post-TMS alone, without CILT. From Naeser MA, Martin PI, Treglia E, et al. Research with rTMS in the treatment of aphasia. Restor Neurol Neurosci 2010;28:511-29. © 2010. Reprinted with permission from IOS Press.[55]

2 also had a lesion located inferior and posterior to Wernicke's area, in BA 21 and 37. Patient 1 had no lesions in these 3 areas.

The significant increase in activation of the left SMA post-TMS in Patient 1, who improved in naming, is compatible with previous fMRI studies that observed new left SMA activation to be present in aphasia patients with a better outcome.[16,17] This improved LH activation is also compatible with previous studies that have observed better outcome after language therapy to be associated with new perilesional LH activation.[21-24]

Based on their results, Martin et al[50] have suggested minimum criteria for entry into TMS treatment as follows: (1) the patient should have a mean score of at least 3 pictures named correctly on the BNT (without phonemic cueing), tested across 3 test sessions, and (2) the patient should not produce stereotypies in spontaneous speech. Patient 2 would not have met these minimum criteria for entry, as his mean BNT score across 3 test sessions pre-TMS ± SD was only 1.67±1.15 (range, 1–3); and he produced stereotypies during spontaneous speech. One severe nonfluent global aphasia patient with a 1-word phrase length, who did not produce stereotypies, had a good response to the TMS protocol of Naeser et al.[37] She named 4 pictures on the BNT pre-TMS; 7 pictures, at 2-months post-TMS; and 12 pictures, at 8-months post-TMS. The degree of improvement resulted in the patient's ability to have individual speech therapy sessions, leading to continued improvement in naming and communication.

PART 2: TMS PLUS CILT

Background and Rationale

CILT is an intensive speech therapy program shown to significantly improve naming after a series of 10 CILT treatments.[52-54] During CILT, patients are only allowed to respond with verbal naming for a picture (no gestures or writing or sound effects are permitted). An opaque screen is placed on a table where the speech-language pathologist (SLP) is seated on 1 side, and the patient on the other. There is eye contact above the screen, but it is not possible for the patient to use hand gestures or writing to communicate. For example, the patient may be given a series of picture cards, and he must communicate verbally to the therapist, which card he has on his side of the screen and/or ask the SLP if there is a similar card on the other side of the screen. The response required from the patient is gradually increased from single words up to phrases and even sentences.

Results from the Maher et al CILT study[52] showed improvement in naming (BNT), primarily at 1 month follow-up testing (not immediately post-CILT). Their results on the Western Aphasia Battery, Aphasia Quotient, had showed improvement immediately post-CILT and also at 1 month follow-up. Maher[52] suggests that "...the impact of CILT may continue to be active beyond the direct treatment period."[52(p850)] The impact of TMS also continues to be active beyond the direct treatment period, for example, at least 2 months or more post-TMS.[33,36,37,49,50] Combining these 2 forms of therapy (TMS and CILT) may promote maximum gains in naming for chronic aphasia patients.

TMS Plus CILT Treatment Protocol With Nonfluent Aphasia

Patients who have completed Phase 1 and 2 TMS,[33] with good response, were eligible to enter a study by Naeser et al[55] that combined TMS and CILT. The best response RH ROI that was suppressed during Phase 2 TMS was suppressed in the same manner, that is, 1-Hz rTMS for 20 minutes, 90% MT for 10 sessions over a 2-week period (weekdays only). A 3-hour CILT session immediately followed each 20-minute TMS session.

A severe nonfluent aphasia patient, who initially received only the Phase 1 and Phase 2 TMS protocol at 6.5-years poststroke, later participated in TMS plus CILT.[55] This patient participated in TMS and CILT at 12.5-years poststroke (5y, 10mo after the initial TMS series). Prior to TMS plus CILT, her object naming ability was tested 3 times on a set of 250 color pictures. One-third of the color pictures presented as stimulus items for therapy had always been named on pretesting (3/3); one-third she had sometimes named (1–2/3); and one-third she had never named (0/3). During CILT, 6 pictures were presented at a time (2 pictures had always been named at entry pretesting; 2, sometimes; 2, never). A total of 18 pictures were presented during CILT each day (3 sets of 6 pictures each).

Language outcome measures included the BNT and subtests on the BDAE. These tests were administered at baseline pre-TMS (3 times) and at 1- and 6-months post- the 10th treatment in the TMS plus CILT protocol by Naeser et al.[55] Significant improvement was defined as more than 2 SD above baseline.

Naming Probe Testing

To examine changes that might occur during intervention, Naming Probe Testing was also completed. BDAE naming subtests (Actions, Animals, Tools/Implements), the BNT, and the action naming pictures from Druks and Masterson[56] were administered 12 times pre-TMS (including the 3 baseline testings). In addition, immediately post- each CILT session, daily Naming Probe Testing was administered (10 times). After the 10th treatment, Naming Probe Testing was again administered (10 separate times). The time-series data for each test were later analyzed using a double bootstrap method (http://www.stat.wmich.edu/slab/Software/Timeseries.html).[57]

Results for TMS Plus CILT

On the primary language outcome measures, this severe nonfluent aphasia patient improved more than 2 SD on BDAE Action Naming, Tools/Implements, and Single Word Repetition. Improvement in BDAE Action Naming was only ob-served after the second TMS series, where CILT was included (fig 2). These results suggest that additional improvements may be gained when TMS is combined with language therapy, such as CILT, in chronic stroke patients with aphasia.

On Naming Probe Testing, the time-series analysis showed significant improvement on BDAE Action Naming ($P=.035$) and Tools/Implements ($P=.010$). There was a trend toward significant improvement on the Action Naming pictures from Druks and Masterson[56] (mean pre-TMS $\pm$ SD, 6.00±1.48; range, 3–7, and mean post-TMS $\pm$ SD, 7.90±1.73; range, 6–10; $P=.308$).

PART 3: POSSIBLE MECHANISMS AND NEW TMS STUDIES IN APHASIA

Possible Mechanisms

The mechanisms associated with language improvement post-TMS treatments in chronic stroke patients with aphasia are unknown. The presence of a differential effect on naming after suppression of right PTr (facilitation of naming) versus suppression of right POp (impairment of naming) during Phase 1 by Naeser et al[43] in nonfluent aphasia patients may provide some insight regarding the potential role of right POp in aphasia. This differential effect suggests potential for different pathways with posterior language regions (temporo-parietal regions), and different roles for the right PTr versus right POp.

For example, in recent DTI studies[58-60] white matter pathways were observed to follow a more dorsal route between left posterior Broca's area (likely POp; and premotor cortices) and anterior supramarginal gyrus (SMG), via the arcuate fasciculus (AF). However, major pathways between left anterior Broca's area (likely PTr, ventrolateral prefrontal cortex) and left superior temporal gyrus have been observed to follow a more ventral route via the extreme capsule (not via the AF).[58,59] The primary role for the dorsal route in the LH is mainly restricted to sensory-motor mapping of sound to articulation, and higher-order articulatory control of speech,[58] where the POp is connected directly with
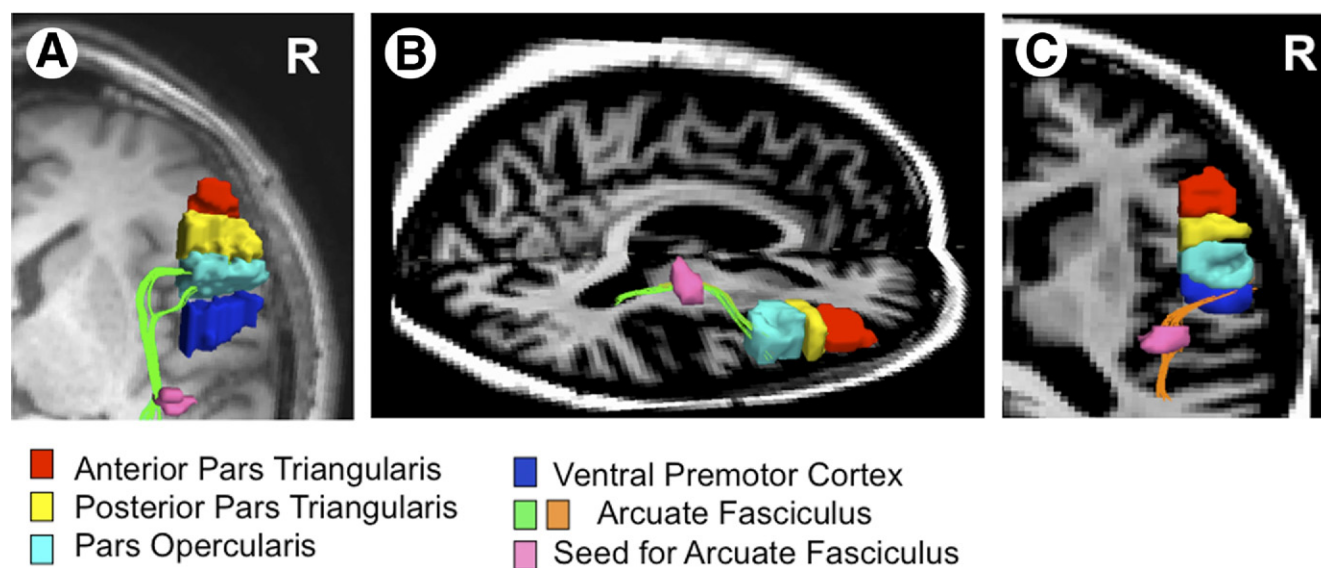

Fig 3. White matter pathways from horizontal, midportion of AF (green) connect primarily with POp (light blue), not posterior PTr (yellow) or anterior PTr (red), in the RH; (a) axial view and (b) sagittal view. (c) White matter pathways from horizontal, midportion of AF (orange) also connect with vPMC (dark blue) in the RH; axial view. The right POp and the right ventral premotor cortical areas are regions that may be important for recovery of speech in chronic stroke patients with nonfluent aphasia. Pink area represents seed point in the horizontal, midportion of the AF in these DTI studies with healthy controls. Abbreviation: R, right.

premotor area 6 (involved with orofacial musculature).[61,62] The ventral route in the LH likely performs linguistic processing of sound to meaning, requiring temporo-frontal interaction and top-down regulation of linguistic processing such as verbal retrieval,[62] and lexical/semantic aspects of language processing.[59,62-67] In support of this, a dissociation between the roles of left PTr and left POp in semantic versus phonologic tasks has been supported by TMS application to these 2 areas in healthy controls, where differential/opposite effects were observed.[68]

Kaplan et al[69] recently studied white matter pathways for the POp and PTr in the RH. Their study observed similar white matter connections in the RH to those reported above in the LH. In most cases, there were no direct pathways between right PTr and right AF, but in most cases, direct pathways were present between right POp and right AF (fig 3). The presence of these different RH pathways may support the differential effect on naming after suppression of right PTr versus right POp in nonfluent aphasia cases. Suppression of right POp with rTMS may have had a direct, negative effect on the phonological aspects of naming and higher-order articulatory control of speech in the nonfluent aphasia patients.

Suppression of right PTr with 1-Hz rTMS may promote less inhibition of right POp from right PTr via U-fibers. Better modulation of right POp may also indirectly support better modulation of right ventral premotor cortex (vPMC), located 1 gyrus posterior to POp. A contributory role for the right POp and the right vPMC in aphasia recovery has been posited since the time of Barlow (1877).[70] Current rTMS data support a contributory role for right POp in aphasia recovery because suppression of right POp impaired naming. In fact, Naeser et al[33,36,37,43] have never observed the right POp to be a best response ROI to improve naming.

Finally, it is worth considering that the POp and vPMC are part of the bilateral mirror neuron system.[71] Mirror neurons are cells that fire during both production and perception of similar actions. They are important in child language acquisition,[72] and they are thought to be present bilaterally. The right POp and right vPMC may have relevance in promoting recovery in aphasia (especially in phonological and motor aspects of speech), due to the presence of mirror neurons. This could help to clarify why suppression of right POp in nonfluent aphasia patients impaired naming, that is, there was possibly interrupted activation of some mirror neurons in this area; however, this is unknown and the unique role of right POp and vPMC in aphasia recovery requires further study.

New TMS Studies in Aphasia

Recent research by Barwood et al[73] used rTMS to suppress the apical portion of right PTr for 2 weeks in chronic nonfluent aphasia patients, in a manner similar to the Phase 2 rTMS treatment protocol by Naeser et al.[33,36,37] Similar results were observed. Significant improvements were observed in BDAE naming Actions, BDAE naming Tools/Implements, BDAE overall score, and BDAE picture description at 2-months post-real rTMS treatment. Importantly, these investigators found no significant improvements at 2-months post-sham rTMS.

Weiduschat et al[74] obtained positron emission tomography scans before and after rTMS combined with conventional speech therapy in a variety of subacute stroke patients with aphasia. Language results showed a significant improvement in total Aachen Aphasia Test scores in cases who received rTMS to suppress the right PTr, plus speech therapy, versus those who received control rTMS to suppress the vertex, plus speech therapy. Positron emission tomography results showed that cases who had received the control rTMS retained a right lateralization of brain activation during verb generation; whereas, those cases who received rTMS over right PTr, no longer retained right lateralization and there was greater improvement in language.

CONCLUSIONS

In summary, the TMS studies by Naeser et al,[33,36,37,49] as well as these new TMS studies,[73,74] all suggest that use of 1-Hz rTMS for a series of at least 10 rTMS treatments results in significant improvement in naming, and often in phrase length during propositional speech. These improvements are long-lasting, up to 2 months, or even as long as 2 years, post-TMS.[33,36,37,49,50] Functional imaging studies report significant improvement in naming in those cases with new LH activation[50] or a shift to overall LH lateralization.[74] When TMS is combined with speech therapy, additional improvement has been observed, beyond TMS alone.[55,74] Additional TMS studies in aphasia are likely to replicate and expand these findings.

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