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Transcranial Magnetic Stimulation Combined With Multimodality Aphasia Therapy for Chronic Poststroke Aphasia

A Randomized Clinical Trial

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Abstract

Background and Objectives

Intensive speech therapy may improve recovery from poststroke aphasia. Further evidence suggests that pairing repetitive transcranial magnetic stimulation (rTMS) with intensive speech therapy might augment outcomes. This sham-controlled randomized clinical trial evaluated the efficacy of 1-Hz rTMS over the right pars triangularis combined with multimodality aphasia therapy (M-MAT) in chronic poststroke aphasia.

Methods

A parallel-group, double-blind, sham-controlled randomized clinical trial was conducted between April 2021 and May 2023 at an outpatient neurorehabilitation clinic. Individuals with chronic nonfluent aphasia after left middle cerebral artery stroke (>6 months from stroke) were enrolled and randomly assigned to receive either rTMS or sham stimulation combined with 35 hours of M-MAT over 10 days. The primary outcome was the Western Aphasia Battery aphasia quotient (WAB-AQ) measured at 3 weeks and 15 weeks. Intention-to-treat analysis examined treatment effects over time using linear mixed models.

Results

A total of 44 participants were randomized. Forty-three (mean [SD] age, 63.4 [12.3] years; 14 women [32.6%]) completed the intervention. Overall, WAB-AQ scores improved from baseline to 15 weeks regardless of rTMS allocation (mean difference 5.33, 95% CI 2.9–7.8, $p < 0.001$). We observed a significant group-by-time interaction ($\beta = 0.31$, $p = 0.024$), suggesting that those who received rTMS combined with M-MAT improved more over time than those who received sham. At 15 weeks, the rTMS group demonstrated significantly less word-finding difficulties and more complete and longer sentences with fewer pauses compared with sham as indicated by higher WAB-AQ scores (mean difference 4.1 points, 95% CI 0.6–7.6, $p = 0.022$). The change from baseline at 15 weeks was greater in the rTMS group (7.6 points, 95% CI 4.1–11.1) compared with sham (3.0 points, 95% CI −0.3 to 5.2; mean difference 4.6 points, 95% CI 0.6–8.6, $p = 0.024$).

Discussion

Intensive administration of M-MAT alone improves speech production in patients with chronic poststroke aphasia. Combining 1-Hz rTMS with M-MAT is associated with supplemental improvements in aphasia severity at follow-up. rTMS is a promising candidate as an adjuvant therapy to M-MAT.

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Class of Evidence
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Glossary

AE = adverse event; **CETI** = Communication Effectiveness Index; **M-MAT** = multimodality aphasia therapy; **rTMS** = repetitive TMS; **SADQ** = Stroke Aphasic Depression Questionnaire; **SAE** = serious AE; **SAQOL-39g** = Stroke and Aphasia Quality of Life Scale; **SLP** = speech-language pathologist; **SLT** = speech and language therapy; **TMS** = transcranial magnetic stimulation; **WAB** = Western Aphasia Battery–Revised; **WAB-AQ** = WAB aphasia quotient.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT04102228.

Classification of Evidence

This study provides Class III evidence that in patients with aphasia 6 or more months after a stroke, 1-Hz rTMS combined with intensive M-MAT improves WAB-AQ more than sham stimulation plus M-MAT.

Introduction

Impairments in language processing, or aphasia, are common after stroke, affecting approximately one-third of patients acutely.[1] It is estimated that half of those who experience aphasia acutely will continue to experience communication disability in the chronic phase of recovery.[2] Poststroke aphasia has been associated with increased rates of depression and diminished quality of life compared with stroke survivors without aphasia.[3,4] Losing the ability to communicate is profoundly life altering and harmful to overall well-being. Speech and language therapy (SLT) is the most effective treatment of poststroke aphasia.[5,6] However, functional recovery from aphasia after SLT is highly variable, often minimal, and effect sizes are modest.[6] Novel therapeutic approaches for chronic poststroke aphasia are needed.

Noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have emerged as potential adjuvant therapies to enhance the efficacy of SLT. rTMS can modulate the excitability of specific cortical regions by applying rapidly changing magnetic fields that induce brief cortical currents.[7] The frequency at which rTMS pulses are delivered can dictate the neuromodulatory effects. For instance, low-frequency (i.e., 1-Hz) rTMS has been associated with downregulation or inhibition of cortical activity.[8] In the context of poststroke aphasia recovery, functional recruitment of spared left hemisphere structures has often been associated with better language recovery than compensatory recruitment of right hemisphere networks.[9-14] Consequently, inhibitory rTMS over the right hemisphere homolog of Broca's area (i.e., pars triangularis) has been used alone or in combination with SLT to improve speech production in poststroke aphasia on the basis of limiting compensatory recruitment of the unaffected hemisphere.[15-19]

Several meta-analyses of a few small randomized controlled trials have reported significant effects of contralesional inhibitory rTMS on aphasia recovery in both subacute and chronic stroke.[20-23] A recent multicenter trial demonstrated improved naming in those who received 1-Hz rTMS with SLT compared with sham stimulation in subacute poststroke aphasia.[24] An extension of the same trial compared rTMS in combination with SLT in subacute vs chronic stroke and found that while both groups improved over time, supplemental gains in naming related to rTMS were only detected in those in the subacute phase of recovery.[25] However, neuromodulation may still be beneficial as an adjuvant to SLT in the chronic phase of recovery with an optimized treatment protocol.

It is important to deliver SLT with sufficient dosage and intensity to achieve the greatest amount of speech improvement.[26] Pairing rTMS with intensive SLT programs such as melodic intonation therapy,[27] constraint-induced aphasia therapy,[28] intensive language action therapy,[29] or multimodality aphasia therapy (M-MAT)[30] may yield superior outcomes compared with intensive SLT alone in chronic poststroke aphasia. However, evidence for combining these therapies is mixed and limited.[31,32] In a pilot study, we demonstrated that inhibitory rTMS followed by 3.5 hours of M-MAT per day for 10 days was safe and feasible in chronic poststroke aphasia.[33]

We conducted a randomized controlled trial to assess the effectiveness of combining 1-Hz inhibitory rTMS with a 2-week intensive dose (35 hours) of M-MAT compared with sham stimulation with M-MAT in a larger cohort of individuals with chronic poststroke nonfluent aphasia. We hypothesized that 1-Hz rTMS in combination with M-MAT would demonstrate significantly greater improvements in aphasia severity compared with those who received sham stimulation plus M-MAT.

Methods

Participants

Participants were recruited from both outpatient neurorehabilitation clinics and the local community between April

2021 and May 2023. Inclusion criteria were as follows: (1) age 18 years or older; (2) left hemisphere stroke at least 6 months before participation; (3) nonfluent aphasia as determined by the Western Aphasia Battery–Revised (WAB)[34] bedside test (fluency score ≤5); (4) first or primary language of English; and (5) ability to follow 3-step commands, to select individuals with greater expressive than receptive language deficits. Exclusion criteria were as follows: (1) previous stroke involving the right frontal lobe, (2) moderate-to-severe depression as measured with the Stroke Aphasic Depression Questionnaire 10-item (SADQ-10),[35] (3) severe verbal apraxia as measured by the Apraxia Battery for Adult (defined as a rating of severe on increasing word length and diadochokinetic rate or utterance time for polysyllabic word subtests) to select those with language-processing impairment rather than motor speech impairment,[36] (4) concurrent diagnosis of any other psychiatric or neurologic disorders, (5) contraindication to MRI or TMS (e.g., implanted cardiac devices), (6) having received intensive speech therapy within the past 6 months (i.e., more than 8 hours per week), or (7) concurrent enrollment in another interventional study.

Randomization and Blinding

This study was a double-blind, sham-controlled, parallel-group randomized controlled trial. Eligible participants were randomized to receive either rTMS or sham stimulation (1:1 allocation ratio) in combination with M-MAT using the web-based randomization module within Research Electronic Data Capture (REDCap). Randomization used a prespecified list of randomly permuted block sizes of 6 for group balance while also accommodating a maximum M-MAT group size of 6 participants. The study statistician generated the random allocation sequence and kept it confidential to ensure concealment of the randomization order and allocation assignment. Participants and members of the study team (speech-language pathologists [SLPs] who administered M-MAT and outcome assessments, and principal and co-investigators) were blinded to the randomization. Study staff who administered rTMS were not blinded to intervention assignments but did not perform outcome assessments or administer M-MAT.

Intervention Overview

Participants underwent baseline speech and language assessments and MRI within 1 week before intervention. Over a 10-day period, participants in small groups of 4–6 received rTMS (or sham) at 1 of 2 laboratories with identical equipment (i.e., 2–3 participants at each location) followed by 3.5 hours of M-MAT. The order of rTMS administration each day was counterbalanced to account for the delay between rTMS administration and the M-MAT session. Each TMS laboratory was supplied a tablet device with Tactus Therapy Naming and Advanced Naming apps installed (Tactus Therapy Solutions Ltd., Vancouver, British Columbia). All participants were trained by our treatment therapists on how to use these apps independently while they were either waiting to receive rTMS or waiting between their rTMS treatment and moving to the M-MAT session. After rTMS, all participants gathered in a single room with 2 study-trained SLPs to undergo M-MAT. Speech and language assessments and MRI were repeated within 1 week after intervention completion (i.e., the 3-week time point) and again at the 15-week time point.

Repetitive Transcranial Magnetic Stimulation

TMS was performed using a Magstim Super Rapid 2 stimulator equipped with an AirFilm coil (Magstim, Cardiff, United Kingdom). Repetitive stimulation was administered while targeting the pars triangularis of the right inferior frontal gyrus using real-time neuronavigation with each participant's T1-weighed image (Brainsight2; Rogue Research, Montreal, Quebec). The target site was localized by identifying the triangular-shaped gyrus bounded by the anterior ramus and ascending ramus of the Sylvian fissure. Pulses were delivered at 100% of resting motor threshold and a frequency of 1 Hz for 20 minutes (i.e., 1,200 pulses). Sham stimulation was achieved using a Magstim sham coil that looks, feels, and sounds the same as the active coil but does not deliver active stimulation.

Multimodality Aphasia Therapy

M-MAT sessions were delivered in a group setting by study-trained SLPs for 3.5 hours per day, 5 days a week for 2 weeks (35 hours), with an additional 15 minutes of daily home practice tasks. Rest breaks of 15 minutes were provided between every 1 hour of therapy. M-MAT involved structured communication activities such as requesting items, recalling items from memory, and naming items. Participants observed the performance of others, took turns, and interacted with each other during tasks. A set of 80 line-drawn picture cards (40 nouns, 40 verbs) was used during therapy while a smaller testing set of 20 images (10 nouns, 10 verbs) was reserved for outcome assessment. Therapists prescribed production targets ranging from single nouns/verbs to complex sentences, cueing and shaping verbal and nonverbal (e.g., gestural, written, or drawn) responses using a detailed cueing hierarchy.[30,37] Drawing and writing were used but were not required if the participant was able to successfully generate the word after gestural, semantic, or phonemic cueing.

Outcome Assessment

Outcome measures were assessed by blinded SLPs at baseline, 3 weeks, and 15 weeks. The primary outcome measure was the WAB aphasia quotient (WAB-AQ).[34] Secondary outcomes included word retrieval (80 treated and 20 untreated images with similar familiarity and frequency of use), functional communication as rated on the Communication Effectiveness Index (CETI),[38] multimodal communication (Scenario Test),[39] mood measured using the SADQ,[35] and quality of life measured using the Stroke and Aphasia Quality of Life Scale (SAQOL-39g).[40] Metrics from the Apraxia Battery for Adults[36] were only used for screening purposes and not as outcome measures.

Serious adverse events (SAEs) such as seizures and adverse events (AEs) including new or worsening headache, pain at the stimulation site, and muscle pain of temporal or neck muscles during or after sessions were documented each

intervention day. Cumulative AEs and SAEs during the 10-day intervention period are reported.

Statistical Analysis

At the time of study design, a 5-point change on the WAB-AQ was considered clinically meaningful.[41] Therefore, this study was powered to detect a between-group difference of 5 points on the WAB-AQ, assuming a SD of 15 and correlation between measurements of 0.9. A predicted target sample size of 46 was inflated to 50 to account for attrition. However, recruitment ended after enrolling 44 participants because lower-than-expected recruitment rates were achieved during the coronavirus disease 2019 pandemic.

Statistical analyses were conducted using R software (version 4.3.1). Analyses for all outcome measures were conducted on an intention-to-treat basis. Baseline demographics and clinical characteristics were compared between groups using a 2-sample *t* test or Mann-Whitney *U* test for continuous data and the Fisher exact test for categorical data. We used a linear mixed model to compare the primary outcome (WAB-AQ) between groups immediately after intervention and at 15 weeks. Group differences were assessed by a group-by-time interaction. The model included covariates for baseline WAB-AQ, age at intervention, and sex. Random effects were specified for the participant to account for repeated measurements and for the cohort to account for clustering within intervention cohorts. Secondary outcomes were analyzed in a similar fashion with CETI, Scenario Test, SAQOL-39g, SADQ, or picture naming as the outcome measure; fixed effects for the treatment group, time, group-by-time interaction, baseline aphasia severity (WAB-AQ), age at intervention, and sex; and random effects for the participant. In cases where the group-by-time interaction was significant, Johnson-Neyman tests were conducted. In brief, the Johnson-Neyman test reports the value or values of the moderator (i.e., time) at which the effect of the predictor (i.e., treatment group) on the dependent variable (e.g., WAB-AQ) was significant.[42,43] The time variable was dummy-coded as continuous rather than categorical to perform the Johnson-Neyman analysis. A secondary per-protocol analysis was conducted using the same methods. Safety and blinding outcomes were examined using Fisher exact tests.

Standard Protocol Approvals, Registrations, and Patient Consents

This trial was approved by the University of Calgary conjoint health research ethics board (REB18-0829) and registered at ClinicalTrials.gov (NCT04102228); the trial protocol and statistical analysis plan are provided in eSAP 1 and eSAP 2, respectively. Written informed consent was obtained before participation.

Data Availability

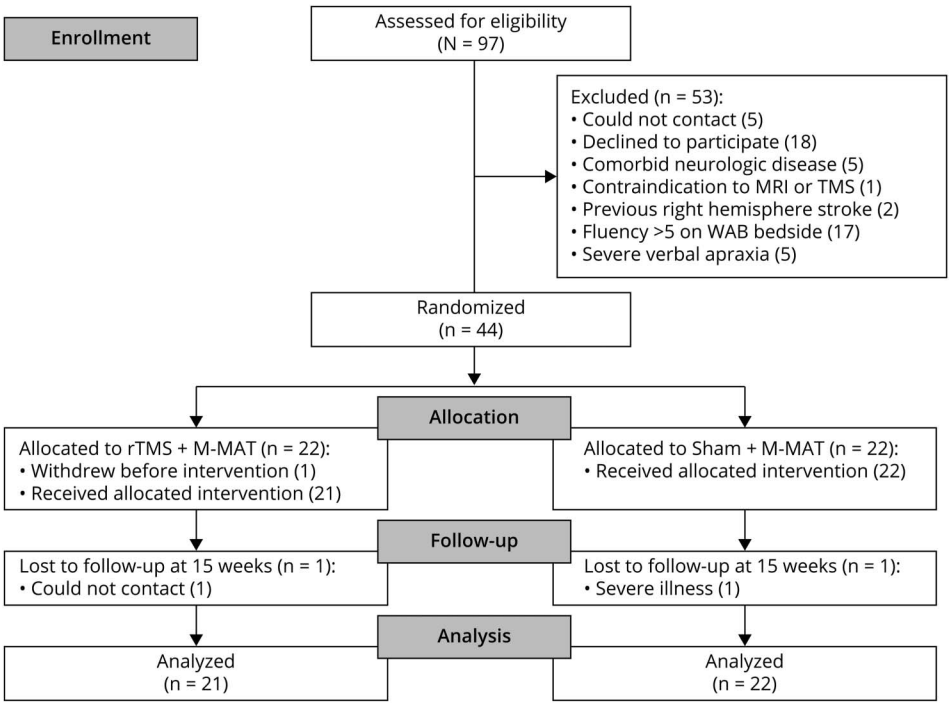
Anonymized data are available on reasonable request from the corresponding author.

Results

Recruitment and Retention

We screened 97 potential participants for eligibility between May 2021 and May 2023 (follow-up completed in August 2023). Of those, 44 eligible participants consented to the trial

Figure 1 Participant Flow Diagram



M-MAT = multimodality aphasia therapy; rTMS = repetitive TMS; TMS = transcranial magnetic stimulation; WAB = Western Aphasia Battery–Revised.

and were randomized (Figure 1). One participant in the rTMS group withdrew before starting the intervention, and 1 participant from each group was lost to follow-up at the 15-week interval. Baseline demographic and clinical characteristics are summarized in Table 1. The average age at intervention was 63.4 years (SD = 12.3), and the mean time since stroke was 4.0 years (SD = 3.7). Groups were broadly similar at baseline although the rTMS group was more fluent compared with sham, as measured by the WAB bedside test. In addition, lesion volumes and locations were similar between groups (Figure 2).

Speech and Language Outcomes

On the primary outcome measure (WAB-AQ), the slope of estimated change for sham (0.20, 95% CI 0.01–0.39) and rTMS (0.51, 95% CI 0.32–0.70) was positive in both groups. Overall, WAB-AQ scores improved from baseline to 15 weeks across both groups (mean difference 5.33 points, 95% CI 2.9–7.8, $p < 0.001$). In addition, we observed a significant group-by-time interaction (β = 0.31, 95% CI 0.05–0.57, $p = 0.024$). To better understand this interaction, we conducted a Johnson-Neyman test, which revealed that the association between the treatment group and WAB-AQ scores was significant at 15 weeks. These results suggest that administration of rTMS plus M-MAT was associated with improved aphasia severity compared with sham, but only at the 15-week interval (Figure 3A). This finding was supported by higher WAB-AQ scores in the rTMS group at the 15-week interval (mean difference 4.1 points, 95% CI 0.6–7.6, $p = 0.022$). Moreover, the change from baseline at 15 weeks was significantly greater in the rTMS group (7.6 points, 95% CI 4.1–11.1) compared with sham (3.0 points, 95% CI −0.3 to 5.2; mean difference 4.6 points, 95% CI 0.6–8.6, $p = 0.024$; Figure 3B and Table 2).

Changes from baseline for each subtest of the WAB are summarized in Table 2. Both groups demonstrated significant improvement over time on spontaneous speech (β = 0.16, 95% CI 0.09–0.23, $p < 0.001$), repetition (β = 0.03, 95% CI 0.01–0.06, $p = 0.008$), and naming and word finding (β = 0.06, 95% CI 0.03–0.08, $p < 0.001$) but not on auditory and verbal comprehension (β = 0.00, 95% CI −0.02 to 0.03, $p = 0.72$). In addition, we observed significant group-by-time interactions for naming and word-finding (β = 0.05, 95% CI 0.01–0.08, $p = 0.015$) and repetition (β = 0.04, 95% CI 0.00–0.07, $p = 0.034$) subtests. Johnson-Neyman testing again identified that the association between the treatment group and improvement on WAB subtests for naming and repetition was significant only at the 15-week interval.

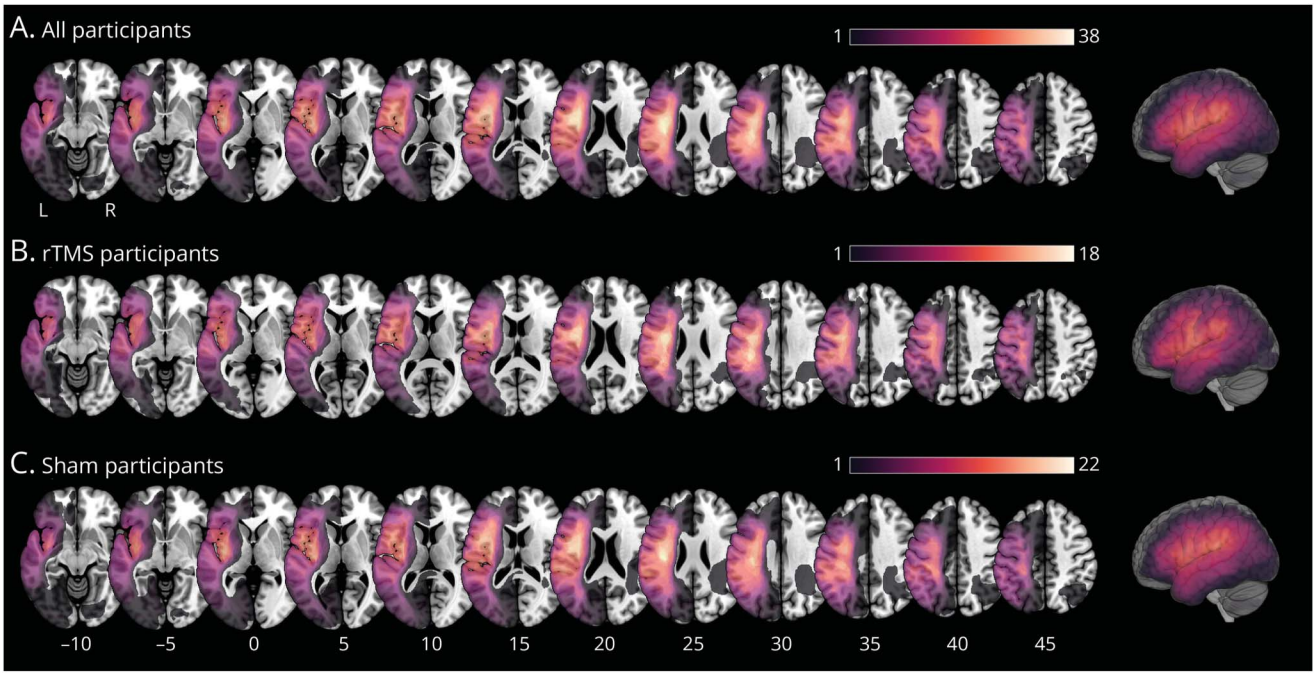
Table 3 summarizes changes from baseline for secondary outcomes. Both sham and rTMS groups demonstrated improvement over time on trained naming (β = 0.54, 95% CI 0.25–0.84, $p < 0.001$), untrained naming (β = 0.14, 95% CI 0.05–0.23, $p = 0.003$), multimodal communication (Scenario Test; β = 0.23, 95% CI 0.03–0.43, $p = 0.023$), and functional communication (CETI; β = 0.42, 95% CI 0.04–0.80, $p = 0.04$). There were not any significant group-by-time interactions for any secondary outcomes. Functional communication differed between groups at baseline (β = 12.9, 95% CI 3.06–22.7, $p = 0.017$); however, the change in CETI scores did not differ between rTMS and sham (β = 0.38, 95% CI −0.16 to 0.92, $p = 0.17$) groups. Mood (SADQ) and quality of life (SAQOL) scores did not significantly differ over time or between groups.

Table 1 Baseline Participant Demographics and Clinical Characteristics

	Sham (n = 22)	rTMS (n = 21)	Test statistic	*p* Value
Age at intervention, y, mean (SD)	64.9 (10.5)	61.8 (14.0)	$t = 0.83$	0.41
Years since stroke, mean (SD)	4.5 (4.1)	3.5 (3.2)	$t = 0.94$	0.35
Sex, M:F, n	15:7	14:7	Fischer exact	1.00
Ethnicity, Caucasian, n (%)	18 (81.8)	19 (90.5)	Fischer exact	0.66
Ischemic strokes, n (%)	19 (86.3)	14 (66.7)	Fischer exact	0.16
Lesion volume, mL, mean (SD)	134.1 (73.8)	107.4 (80.9)	$t = 1.13$	0.27
WAB bedside fluency, median (range)	2 (0–5)	4 (1–5)	$U = 148.5$	0.04[a]
Diadochokinetic rate, mean (SD)	9.4 (9.4)	9.7 (8.0)	$t = 0.10$	0.92
Utterance time for polysyllabic words, s, mean (SD)	59.4 (27.7)	51.3 (29.0)	$t = 0.94$	0.35
Increasing word length score, mean (SD)	3.4 (4.0)	4.7 (3.3)	$t = 1.36$	0.18

Abbreviations: rTMS = repetitive transcranial magnetic stimulation; WAB = Western Aphasia Battery–Revised.
Diadochokinetic rate measured by the Apraxia Battery for Adults represents the mean number of repetitions within timed trials for 2-syllable and 3-syllable sounds; higher scores indicate less apraxia. Utterance time for polysyllabic words represents the total time from initiation of an attempt at the target word to its successful completion for 10 trials, with a maximum time of 100 seconds (limit of 10 seconds per trial); lower scores indicate less apraxia. Increasing word length score provides a measure of performance deterioration between words of increasing length (e.g., thick, thicken, and thickening); lower scores indicate less apraxia.
[a] Statistical significance at $p < 0.05$.

Figure 2 Lesion Overlap Image Showing the Number of Participants With a Lesion in Each Voxel Overlaid on an MNI Standard Template Image



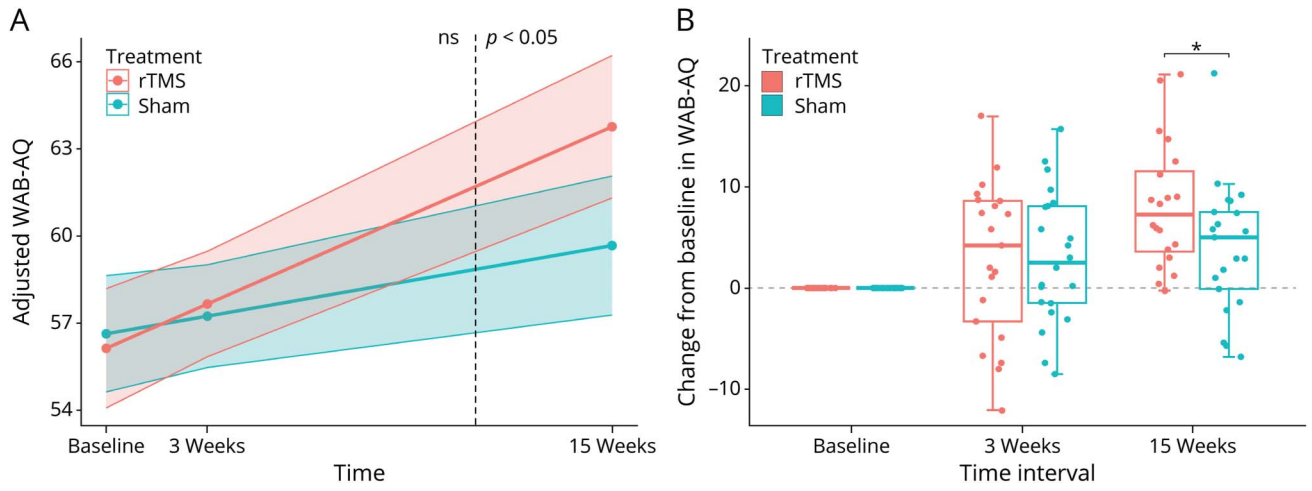
MNI = Montreal Neurological Institute; rTMS = repetitive transcranial magnetic stimulation.

None of the intention-to-treat analysis findings or conclusions were altered by the secondary per-protocol analysis.

Safety

AEs were rare and mild. The most frequent AEs were mild headaches after stimulation (sham n = 10/216 sessions; rTMS n = 10/206 sessions). Some individuals reported tingling sensations near the target site or in the right upper extremity after stimulation (sham n = 9/216 sessions; rTMS n = 4/206 sessions). The total number of AEs over the course of the 10-day intervention did not differ between groups (sham n = 27/216 sessions; rTMS n = 21/206 sessions; Fisher exact, $p = 0.448$). No SAEs occurred. There was no association between participant guess at whether rTMS or sham was

Figure 3 Changes in Primary Outcome Measures Over Time



(A) Adjusted mean aphasia severity (WAB-AQ) over time. The dashed vertical line indicates the upper bound of the Johnson-Neyman interval, which specifies the point in time where the group-by-time interaction is deemed to be significant. Colored ribbons indicate 95% confidence intervals. (B) Unadjusted change from baseline in WAB-AQ at 3 and 15 weeks in rTMS and sham groups. *Statistical significance at $p < 0.05$. rTMS = repetitive transcranial magnetic stimulation; WAB-AQ = Western Aphasia Battery–Revised aphasia quotient.

Table 2 Primary Outcome Measure Changes Compared With Baseline After 2 Weeks of M-MAT Plus rTMS or Sham Stimulation

Primary outcome	Adjusted mean change vs baseline (95% CI)			Adjusted mean difference between sham and rTMS (95% CI)	*p* Value
	Total (n = 43)	Sham (n = 22)	rTMS (n = 21)		
WAB-AQ					
Baseline, mean (95% CI)[a]	56.7 (55.2 to 58.2)	56.9 (54.9 to 59.0)	56.4 (54.3 to 58.6)	0.50 (−2.46 to 3.46)	0.74
3 wk	1.07 (0.58 to 1.56)[b]	0.61 (−0.1 to 1.3)	1.53 (0.8 to 2.2)[b]	0.92 (0.12 to 1.71)	—
15 wk	5.33 (2.89 to 7.78)[b]	3.04 (−0.4 to 6.5)	7.63 (4.1 to 11.1)[b]	4.59 (0.62 to 8.57)[c]	0.024
WAB subtests					
Spontaneous speech					
Baseline, mean (95% CI)[a]	10.4 (9.86 to 11.0)	10.4 (9.60 to 11.2)	10.5 (9.64 to 11.3)	0.08 (−1.09 to 1.24)	0.89
3 wk	0.33 (0.15 to 0.52)[b]	0.19 (−0.07 to 0.46)	0.48 (0.21 to 0.75)	0.28 (−0.02 to 0.59)	—
15 wk	1.67 (0.73 to 2.61)[b]	0.96 (−0.35 to 2.28)	2.38 (1.03 to 3.73)	1.42 (−0.11 to 2.95)	—
Auditory verbal comprehension					
Baseline, mean (95% CI)[a]	7.21 (7.00 to 7.42)	7.15 (6.85 to 7.44)	7.27 (6.97 to 7.57)	0.12 (−0.30 to 0.55)	0.57
3 wk	0.05 (−0.02 to 0.11)	0.08 (−0.01 to 0.17)	0.01 (−0.08 to 0.11)	0.06 (−0.04 to 0.17)	—
15 wk	0.23 (−0.10 to 0.56)	0.39 (−0.06 to 0.84)	0.07 (−0.31 to 0.42)	0.32 (−0.21 to 0.86)	—
Repetition					
Baseline, mean (95% CI)[a]	5.46 (5.29 to 5.63)	5.51 (5.28 to 5.75)	5.41 (5.16 to 5.65)	0.11 (−0.23 to 0.44)	0.53
3 wk	0.04 (−0.02 to 0.10)	−0.01 (−0.09 to 0.07)	0.10 (0.01 to 0.18)	0.11 (0.01 to 0.20)	—
15 wk	0.22 (−0.08 to 0.52)	−0.05 (−0.45 to 0.36)	0.48 (0.06 to 0.90)	0.53 (0.04 to 1.02)[c]	0.034
Naming and word finding					
Baseline, mean (95% CI)[a]	5.28 (5.08 to 5.48)	5.29 (5.01 to 5.57)	5.27 (4.99 to 5.56)	0.01 (−0.41 to 0.38)	0.38
3 wk	0.11 (0.04 to 0.18)[b]	0.04 (−0.06 to 0.13)	0.18 (0.08 to 0.28)[b]	0.14 (0.03 to 0.25)	—
15 wk	0.54 (0.20 to 0.89)[b]	0.19 (−0.28 to 0.67)	0.89 (0.41 to 1.38)[b]	0.70 (0.14 to 1.26)[c]	0.015

Abbreviations: M-MAT = multimodality aphasia therapy; rTMS = repetitive transcranial magnetic stimulation; WAB = Western Aphasia Battery–Revised; WAB-AQ = Western Aphasia Battery–Revised aphasia quotient.
[a] Baseline rows display the adjusted mean (95% CI) for each group and the adjusted mean difference between groups.
[b] Statistically significant within-group change from baseline.
[c] Statistically significant between-group difference.
The symbol "—" indicates that that the test was not performed because there was not a significant interaction or the time point was within the Johnson-Neyman region of nonsignificance.

received; 64% of those assigned to sham and 86% of rTMS participants believed that they received active rTMS (Fisher exact, $p = 0.162$).

Classification of Evidence

This study provides Class III evidence that in patients with aphasia 6 or more months after a stroke, 1-Hz rTMS combined with intensive M-MAT improves WAB-AQ more than sham stimulation plus M-MAT.

Discussion

In this randomized sham-controlled trial, M-MAT was associated with longitudinal improvement on the WAB-AQ and secondary outcomes of naming, functional communication, and multimodal communication regardless of rTMS allocation. An adjunctive effect of 1-Hz rTMS targeting the right pars triangularis coupled with M-MAT was observed with enhancement of aphasia recovery compared with sham stimulation plus M-MAT at the 15-week follow-up.

Improvement in communication irrespective of rTMS allocation in this study is indicative of the potential efficacy and importance of a brief but high-dose, high-intensity delivery of SLT such as M-MAT in the rehabilitation of chronic poststroke aphasia.[26] Numerous case studies and small trials have indicated that low-frequency rTMS is beneficial in poststroke aphasia either as a standalone intervention or in combination with low-dose SLT.[20-23] More recently, a multicenter trial of low-frequency rTMS combined with 45 minutes of SLT per day for 10 days in

Table 3 Secondary Outcome Measure Changes Compared With Baseline After 2 Weeks of M-MAT Plus rTMS or Sham Stimulation

Secondary outcomes	Adjusted mean change vs baseline (95% CI)			Adjusted mean difference between sham and rTMS (95% CI)	*p* Value
	Total (n = 43)	Sham (n = 22)	rTMS (n = 21)		
Naming battery (trained)					
Baseline, mean (95% CI)[a]	42.2 (38.0 to 46.4)	41.1 (35.3 to 46.9)	43.4 (37.4 to 49.4)	2.29 (−6.0 to 10.6)	0.58
3 wk	1.29 (0.50 to 2.07)[b]	0.94 (−0.17 to 2.05)	1.63 (0.52 to 2.74)[b]	0.69 (−0.59 to 1.97)	—
15 wk	6.43 (2.54 to 10.4)[b]	4.70 (−0.84 to 10.2)	8.15 (2.58 to 13.71)[b]	3.44 (−2.95 to 9.83)	—
Naming battery (untrained)					
Baseline, mean (95% CI)[a]	9.84 (8.77 to 10.9)	10.0 (8.5 to 11.5)	9.7 (8.2 to 11.2)	0.34 (−1.77 to 2.45)	0.74
3 wk	0.30 (0.06 to 0.54)[b]	0.17 (−0.16 to 0.51)	0.43 (0.09 to 0.77)[b]	0.26 (−0.13 to 0.65)	—
15 wk	1.51 (0.32 to 2.70)[b]	0.86 (−0.82 to 2.54)	2.16 (0.47 to 3.85)[b]	1.30 (−0.64 to 3.24)	—
Scenario Test					
Baseline, mean (95% CI)[a]	36.0 (33.2 to 38.9)	34.1 (30.1 to 38.0)	38.0 (33.9 to 42.1)	3.95 (−1.75 to 9.64)	0.17
3 wk	0.89 (0.36 to 1.41)[b]	1.06 (0.33 to 1.79)[b]	0.71 (−0.04 to 1.46)[b]	0.35 (−0.50 to 1.20)	—
15 wk	4.42 (1.82 to 7.03)[b]	5.31 (1.66 to 8.95)[b]	3.54 (−0.19 to 7.28)	1.76 (−2.48 to 6.01)	—
CETI					
Baseline, mean (95% CI)[a]	56.2 (50.9 to 61.4)	49.7 (42.4 to 57.0)	62.6 (55.1 to 70.1)	12.9 (2.39 to 23.4)[c]	0.017
3 wk	0.67 (−0.34 to 1.68)	0.09 (−1.34 to 1.52)	1.25 (−0.18 to 2.67)	1.15 (−0.49 to 2.8)	—
15 wk	3.35 (−1.69 to 8.40)	0.47 (−6.69 to 7.62)	6.24 (−0.71 to 10.7)	5.77 (−2.45 to 14.0)	—
SAQOL					
Baseline, mean (95% CI)[a]	3.26 (3.03 to 3.48)	2.97 (2.66 to 3.28)	3.55 (3.22 to 3.87)	0.57 (0.13 to 1.02)[c]	0.013
3 wk	0.03 (−0.01 to 0.06)	0.03 (−0.02 to 0.08)	0.03 (−0.02 to 0.08)	0.00 (−0.05 to 0.06)	—
15 wk	0.14 (−0.03 to 0.32)	0.15 (−0.09 to 0.39)	0.14 (−0.11 to 0.38)	0.01 (−0.27 to 0.29)	—
SADQ[d]					
Baseline, mean (95% CI)[a]	6.87 (5.63 to 8.10)	7.7 (6.0 to 9.4)	6.0 (4.3 to 7.8)	1.65 (−0.81 to 4.11)	0.18
3 wk	0.18 (−0.08 to 0.44)	0.21 (−0.16 to 0.57)	0.15 (−0.22 to 0.53)	0.06 (−0.37 to 0.48)	—
15 wk	0.91 (−0.40 to 2.21)	1.05 (−0.78 to 2.87)	0.77 (−1.10 to 2.64)	0.28 (−1.85 to 2.41)	—

Abbreviations: CETI = Communication Effectiveness Index; M-MAT = multimodality aphasia therapy; rTMS = repetitive transcranial magnetic stimulation; SADQ = Stroke Aphasic Depression Questionnaire 10-item; SAQOL = Stroke and Aphasia Quality of Life Scale.
[a] Baseline rows display the adjusted mean (95% CI) for each group and the adjusted mean difference between groups.
[b] Statistically significant within-group change from baseline.
[c] Statistically significant between-group difference.
[d] Lower SADQ scores indicate fewer depressive symptoms.
The symbol "—" indicates that that the test was not performed because there was not a significant interaction or the time point was within the Johnson-Neyman region of nonsignificance.

subacute poststroke aphasia observed a delayed benefit of rTMS at 30 days after intervention.[24] However, an extension of this trial comparing subacute and chronic poststroke aphasia revealed that this delayed add-on effect of rTMS was only present in those who received the combined intervention in the subacute phase of recovery.[25] Taken together with our findings, this may suggest that at the chronic stage, rTMS may only have additive benefits when the SLT delivered is of a sufficient dosage and intensity. Furthermore, this may highlight that rehabilitation approaches cannot be one-size-fits-all. While individuals at the subacute phase can see benefit from a lower intensity of SLT, those at the chronic stage may need more intensive interventions to obtain similar improvements. Alternatively, it may be the case that similar improvements are possible after lower intensity interventions in the chronic phase of recovery, but the recovery process is much slower than that of subacute stroke and could not be observed within 30 days of intervention of the NORTHSTAR-CA study.[25] Limited generalization of treatment effects to untrained items and secondary outcomes was consistent with findings from larger SLT trials.[44,45]

In the context of stroke rehabilitation, delayed treatment effects may be even more important than immediate effects, suggesting that a limited course of rTMS combined with high-intensity and high-dosage SLT can result in longer term improvements beyond maintenance of gains. In fact, sustained improvement may be a key characteristic of rTMS as an adjuvant therapy, given that trials evaluating high-intensity SLT tend to see immediate improvements followed by a maintenance of those gains at long-term follow-up rather than continued improvement.[30,44-46] Delayed improvements after rTMS are supported by meta-analyses where the effect sizes tend to increase in strength from immediate post-treatment to follow-up.[23] One potential explanation for delayed effects is that rTMS may initially cause a facilitating effect, which then triggers the strengthening, development, or reorganization of alternate functional pathways for speech.[24] Subsequent use of these pathways over time then results in improved speech performance at longer follow-up intervals. However, it is not yet known how these proposed mechanisms are manifested in the brain, and this necessitates future neuroimaging studies.

Individuals with chronic poststroke aphasia typically receive limited formal speech therapy beyond what is provided as an inpatient in Canada and Australia.[45,47,48] Given the wealth of evidence to suggest that more SLT in the chronic phase is associated with better long-term outcomes,[26,46] improvements in speech production at the chronic phase without adequate therapy are likely minimal. Moreover, administration of outpatient programs can be costly. Therefore, it is promising that a relatively brief 2-week intervention may be able to facilitate longer term improvements in aphasia severity for those in the chronic stage. While intensive programs such as M-MAT may present a substantial cost, some evidence suggests that M-MAT may result in better outcomes with potential cost savings per quality-adjusted life year.[49] Combining rTMS with M-MAT may, therefore, result in greater savings, given larger and more sustained improvements compared with M-MAT alone. However, additional costs for rTMS equipment, maintenance, and staff must also be considered when evaluating the economics of this intervention. Furthermore, larger trials with longer follow-up are required to determine the duration of rTMS-related effects and potential need for maintenance doses.

It is important to acknowledge the limitations of this study. First, we did not achieve our recruitment target of 50 participants with chronic stroke. This highlights the need for future trials with multiple sites. Second, assessment and treatment fidelity measures were not captured in this study, which limits our ability to quantify the intensity of M-MAT delivered or participation in any nontrial interventions during the follow-up period. Future studies should collect these data to improve clinical utility of behavioral findings. Another limitation to consider is that randomization in this study did not stratify by baseline aphasia severity. While we selected for individuals with moderate-to-severe nonfluent aphasia and baseline WAB-AQ performance was similar between groups, future studies should consider this important prognostic factor. Finally, aside from statistical significance, it is challenging to determine the clinical relevance of the observed changes in our primary and secondary outcomes. This is because there is a lack of consensus and patient feedback on what constitutes clinically meaningful gains on speech and language measures.[50]

Contralesional 1-Hz rTMS targeting the right pars triangularis combined with M-MAT is a safe and promising adjuvant therapy for chronic poststroke nonfluent aphasia. While the delivery of M-MAT regardless of rTMS allocation provided improvements in communication, the combination of rTMS with M-MAT resulted in significant supplemental reduction in overall aphasia severity at follow-up. Further investigation of this rTMS protocol should include multiple sites and longer follow-up to establish efficacy and determine the longevity of add-on effects. Future studies should also search for neuroimaging markers that may explain delayed benefits of rTMS, or predictors that would aid in selecting individuals who are likely to benefit from this protocol.

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Author Contributions

T.A. Low: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K. Lindland: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. A. Kirton: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. H.L. Carlson: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. A.D. Harris: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. B.G. Goodyear: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. O. Monchi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M.D. Hill: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. M.L. Rose:

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