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A Pilot Randomized Controlled Trial of Intermittent Theta Burst Stimulation as Stand-Alone Treatment for Post-Stroke Aphasia: Effects on Language and Verbal Functional Magnetic Resonance Imaging (fMRI)

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: There is an ongoing need for facilitating language recovery in chronic post-stroke aphasia. The primary aim of this study (NCT01512264) was to examine if noninvasive intermittent theta burst stimulation (iTBS) applied to the injured left-hemispheric cortex promotes language improvements and fMRI changes in post-stroke aphasia.

Material/Methods: Participants were randomized to 3 weeks of sham (Tx0) or 1-3 weeks of iTBS (Tx123). We assessed participants who completed the first 2 functional MRI (fMRI) sessions (T1, T2) where they performed 2 overt language fMRI tasks, and examined longitudinal response after 3 months (T3). Language performance and fMRI activation changes, and relationships between these changes were assessed.

Results: From T1 to T2, both groups showed improvements on the Boston Naming Test (BNT). From T1 to T3, Tx123 improved on the Aphasia Quotient, post-scan word recognition on the verbal paired associates task (VPAT), and perceived communicative ability. Each group exhibited significant activation changes between T1 and T2 for both tasks. Only the Tx123 group exhibited fMRI activation changes between T2 to T3 on the verb-generation task and between T1 and T3 on VPAT. Delayed aphasia symptom improvement for Tx123 was associated with increased left ventral visual stream activation from T1 to T3 ($\rho=0.74$, $P=0.0058$), and with decreased bilateral supplementary motor area activation related to VPAT encoding from T2 to T3 ($\rho=-0.80$, $P=0.0016$).

Conclusions: Observed iTBS-induced language improvements and associations between delayed fMRI changes and aphasia improvements support the therapeutic and neurorehabilitative potential of iTBS in post-stroke aphasia recovery.

Keywords: **Aphasia • Magnetic Resonance Imaging • Stroke • Transcranial Magnetic Stimulation**

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Background

Post-stroke aphasia has an overall negative effect on a person's quality of life [1] and long-term health outcomes [2]. The current standard of care for the treatment of post-stroke aphasia is speech/language rehabilitation [3], but improvements diminish particularly in the chronic stage of stroke (ie, more than 1 year post-stroke) and with increasing age [4,5]. Few therapies have been developed to augment aphasia recovery, particularly in the chronic stage. Given its significant negative impact, development of strategies to improve recovery in chronic post-stroke aphasia is warranted.

Noninvasive repetitive transcranial magnetic stimulation (rTMS) has shown promise in promoting effective post-stroke language recovery after stroke [6-11]. The majority of rTMS studies have utilized inhibitory low-frequency stimulation (1-4 Hz) applied to the unaffected right hemisphere of patients with post-stroke aphasia [12]. However, excitatory rTMS of above 5 Hz to the language cortex in the left hemisphere of healthy individuals [13] and those with primary progressive aphasia [14] have been shown to improve language performance. Preservation or maintenance of function in the canonical language areas of the left hemisphere is of importance for better post-stroke language recovery [15]. A specific rTMS paradigm called intermittent theta burst stimulation (iTBS), which consists of a 2-second train of TBS repeated every 10 s to deliver 600 pulses over 190 s, has exhibited promise for post-stroke aphasia treatment and neurorehabilitation in previous open-label studies [6,7,11]. This pattern of stimulation mimics that of hippocampal neuronal firing [16] and has been shown to facilitate motor-evoked potentials for at least 1 h after stimulation [17]. Consequently, previous studies applying iTBS to left hemisphere language cortex of aphasia patients have shown improved language performance when iTBS was used as a primer for language therapy [6,11].

Only recently has a randomized, double-blind, sham-controlled trial been conducted to investigate whether stand-alone iTBS applied to the ipsilesional hemisphere improves post-stroke aphasia [10]. Participants who received active iTBS exhibited significant improvements on the Boston Naming Test (BNT) and the semantic fluency test (SFT) from baseline (T1) to immediately post-treatment (T2), and a delayed improvement in the Western Aphasia Battery aphasia quotient (AQ) at 3 months post-treatment (T3) that were not observed in those who received sham iTBS [10]. The current study reports on a subset of these participants who additionally completed 2 overt language fMRI tasks during the same MRI sessions and additional language assessments at least at the first 2 time points, with the primary aim to examine iTBS-induced changes from baseline to immediate post-treatment (T1 vs T2). Secondary aims were to investigate any residual or sustained effects of treatment after 3 months (T2 vs T3) and any potentially delayed or continued improvement

after 3 months compared to baseline (T1 vs T3). Thus, the current study aims to extend our knowledge of the effects of iTBS as a stand-alone treatment for chronic post-stroke aphasia.

Material and Methods

Study design

All study procedures were approved by the Institutional Review Board at the University of Cincinnati (UC) and University of Alabama at Birmingham (UAB) and conducted according to Declaration of Helsinki ethics principles. All participants provided written informed consent. The trial was registered at clinicaltrials.gov (NCT 01512264). We conducted a pilot double-blinded randomized sham-controlled trial of iTBS for the stand-alone treatment of chronic post-stroke aphasia. Prior to initiating the study, randomization envelopes containing group assignments were prepared (**Table 1**). Participants were randomized into 3 weeks sham (Tx0) or iTBS (Tx123; dosing strategies: 1 week iTBS with 2 weeks sham, 2 weeks iTBS with 1 week sham, or 3 weeks iTBS). Only the iTBS treatment staff were not blinded to group assignment, but were blinded to baseline assessment results. The randomization envelope was opened only after motor threshold (MT) determination used to set treatment stimulation parameters. Treatment assignments were revealed only after all participants completed the study. Participants underwent fMRI and language assessments at baseline (T1), within 1 week immediately following treatment (T2), and 3 months after treatment completion (T3).

Participants

Adults ≥ 18 years old who had suffered a single ischemic left middle cerebral artery stroke ≥ 1 year prior to enrollment were recruited. Individuals with pre-stroke English fluency and Token Test scores below the 90th percentile were eligible [18]. Exclusion criteria included receiving language therapy within 3 months prior to enrollment, having an underlying degenerative metabolic disorder, self-reported depression or other psychiatric disorders, contraindications to undergoing 3T MRI or to being administered TMS, and pregnancy or positive urine pregnancy test in women of childbearing age. The CONSORT diagram in **Figure 1A** outlines study recruitment. Of 62 individuals offered participation, 26 declined. Of 36 who consented, 5 were withdrawn after screening (1 experienced a previous seizure, 1 could not undergo fMRI, and 3 scored $>90^{\text{th}}$ percentile on the Token Test). Another 3 were withdrawn for completing less than 2 assessments and were lost to follow-up (no completed fMRI or iTBS). Four of 28 randomized participants did not complete overt fMRI tasks at both T1 and T2 and were not included in analysis. Of the 24 remaining participants, 18 attended all 3 visits (6 did not complete T3). Due

Table 1. Baseline data of stroke participants who completed the overt fMRI language tasks for the first 2 time points and were included in the analyses (N=24). Based on the randomization procedure, the subjects received variable number of sham and active iTBS treatment (Tx) weeks.

Participant	TT	Handedness	Sex	Age at scan	YSS	fMRI sessions	iTBS Tx weeks	Group
PART002	33	Right	M	64.6	14	3	0	Tx0
PART012	21	Right	F	23.8	2.3	2	0	Tx0
PART019	34	Right	F	43.6	2.2	3	0	Tx0
PART023	9	Right	M	54.6	3.7	3	0	Tx0
PART024	41	Left	M	44.1	3.3	3	0	Tx0
PART036	32	Right	M	63	2.2	3	0	Tx0
PART001	28	Right	F	79	3.4	3	1	Tx123
PART010	34	Right	M	43.1	1.3	3	1	Tx123
PART013	10	Right	F	66.6	2.2	3	1	Tx123
PART021	9	Right	M	46.4	1.7	2	1	Tx123
PART030	31	Right	M	84.7	1.3	2	1	Tx123
PART034	12	Right	M	47.3	0.9	3	1	Tx123
PART003	12	Right	F	57.8	13	3	2	Tx123
PART008	9	Right	M	57	2.1	3	2	Tx123
PART022	23	Right	M	53.3	1.2	3	2	Tx123
PART027	24	Right	M	67.4	12.7	2	2	Tx123
PART033	27	Right	M	54	1	2	2	Tx123
PART035	4	Right	M	46.2	1.2	3	2	Tx123
PART006	6	Right	M	49.6	2.9	3	3	Tx123
PART009	21	Right	M	50.7	1.1	3	3	Tx123
PART011	6	Right	F	74	1.65	2	3	Tx123
PART014	39	Left	F	61.8	4.4	3	3	Tx123
PART020	33	Right	M	62.1	2.7	3	3	Tx123
PART032	39	Right	F	57.2	1.1	3	3	Tx123

TT – Token Test score; YSS – years since left hemisphere ischemic stroke.

to the high dropout rate (12/36), all participants treated with active iTBS were combined (Tx123; n=18) and compared to sham (Tx0; n=6). The 24 participants included in analysis are a subset of a larger previously reported study [10].

Assessments

Assessments at T1, T2, and T3 included the Boston Naming Test (BNT) [19], Controlled Oral Word Association Test (COWAT) [20], Semantic Fluency Test (SFT) [20,21], and the Western Aphasia Battery-Revised (WAB-R) to determine Aphasia Quotient (AQ) [22], which were described in a larger previously reported study [10]. Participants were also assessed using the Complex Ideation subset of the Boston Diagnostic Aphasia Examination [23], Peabody Picture Vocabulary Test (PPVT) [24], WAB-R Apraxia Total score [22], and the mini-Communicative Activity Log (mini-CAL) for perception of everyday communicative ability [25].

Transcranial Magnetic Stimulation

Sessions occurred 5 days/week over 3 weeks. Prior to iTBS, resting and active MTs were determined via surface electromyography leads placed over the left first dorsal interosseous muscle. Brainsight's neuronavigation system (Rogue Research, Inc., Montreal, Canada) and structural MRI were used to identify the right hemisphere motor cortex and then apply a single TMS pulse using a Magstim Rapid2® figure-of-8 coil (Magstim Co., Wales, UK). Resting and active MTs were determined by the minimum stimulation intensity that elicited $\geq 50 \mu\text{V}$ and $\geq 200 \mu\text{V}$, respectively, for motor-evoked potential amplitude in at least 5/10 consecutive trials. Results of a semantic-decision/tone-decision task (detailed description in [6] as part of an open-label iTBS trial) whereby a location in and around the left inferior frontal gyrus (IFG) that was most responsive during fMRI was identified and used as the

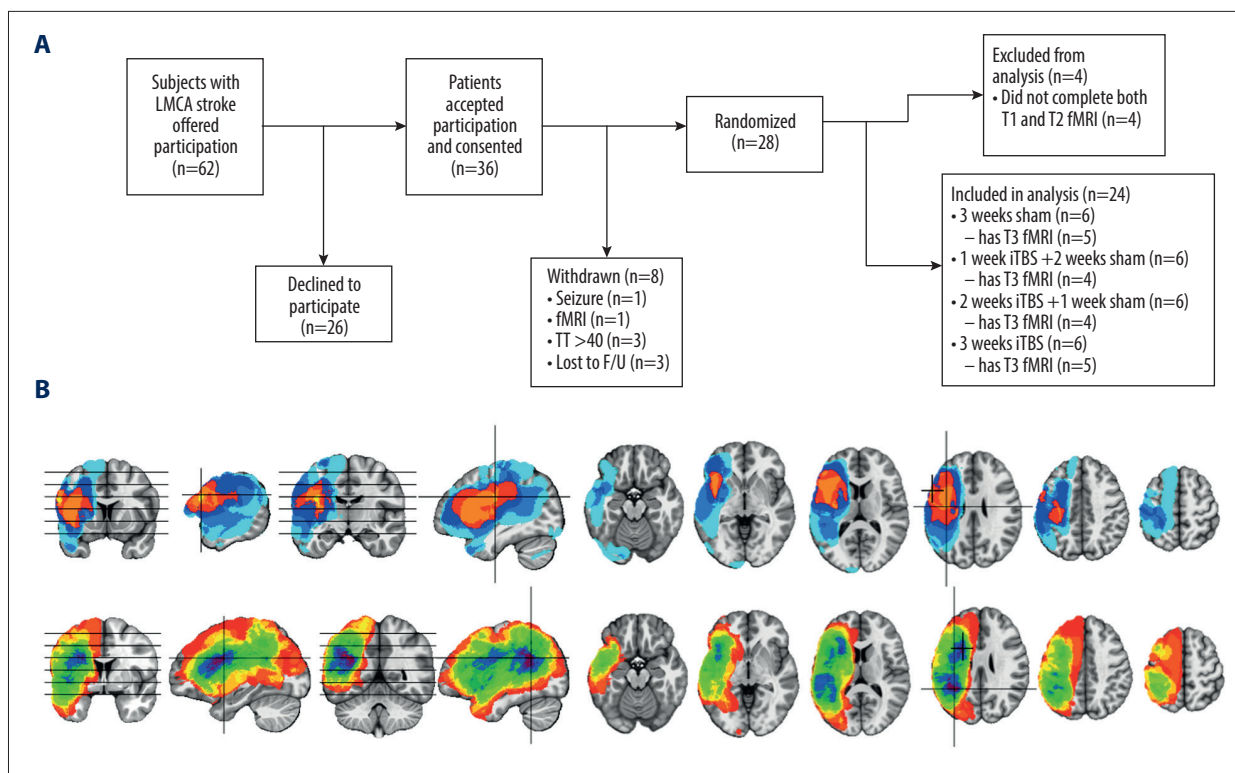


Figure 1. Overview of CONSORT flow diagram (A) and composite lesion maps for the iTBS treatment groups (B). (A) The diagram outlines recruitment of subjects who suffered a left middle cerebral artery (LMCA) stroke and how many participants did and did not complete both fMRI visits at baseline within 1 week of iTBS treatment initiation (T1), within one week of treatment completion (T2), and again after 12 weeks following treatment completion (T3). (B) The composite lesion map color scale for the sham iTBS group (top; n=6) ranges from the minimum (n=1 in light blue) to the maximum (n=6 in yellow) number of participants that show overlap of lesions in 2 locations indicated by the crosshairs in the sagittal and axial slices. The composite lesion map color scale for the active iTBS group (bottom; n=18) ranges from the minimum (n=1 in dark orange) to the maximum (n=14 in maroon) number of participants that show overlap of lesions in 2 locations indicated by the crosshairs in the sagittal and axial slices. Left in the image is left in the brain. The inferior to superior horizontal lines on the coronal images indicates each axial slice from left to right.

iTBS target. A neuroimaging and stroke expert (JPS) blinded to treatment arms reviewed each participant fMRI activation maps and determined the final iTBS target. Once MTs were determined, the randomization envelope was opened, and either the figure-of-8 stimulation or sham coil was used to apply 600 iTBS or sham pulses, respectively over 200 s with intensity set to 80% active MT [6,7,17]. The safety of this approach has previously been determined in stroke patients [6,7]. Participants were monitored for adverse events during and after each session.

Overt Language Functional MRI Tasks

Participants performed 2 overt language tasks during event-related fMRI that were acquired using sparse-sampling acquisition [26]. For each task, stimulus events were presented for 6 s during MRI silence to allow for an overt response to be recorded and then later transcribed. In the following 6 s, 3 fMRI volumes were acquired to capture the peak blood oxygenation

level-dependent (BOLD) response to the prior event trial (ie, task stimulus presentation and overt response) [27].

The verb generation task (VGT) involved auditory presentation of a noun, and participants were presented with visual instructions to either think of verbs related to the noun (“think verbs” for covert verb-generation), say the verbs related to the noun out loud (“say verbs” for overt verb generation), or repeat the noun out loud (“repeat noun” for overt repetition) [27]. The verbal paired associates task (VPAT), involved visual presentation of a pair of related words separated by a hyphen that either rhyme (“bee–tree”), have opposite meanings (“dry–wet”), are synonyms (“large–big”), or are semantically related (“sun–moon”). Participants were instructed to either read aloud or generate the second word out loud [28–30]. For the “read” condition, the second word was provided as in the examples above. For the “generate” condition, only the first letter of the second word was provided followed by asterisks for each remaining letters of the word (eg, “bee–t***”), and participants

Table 2. Variables for the study participants who completed at least the first 2 fMRI visits (T1, T2), and those who returned for a follow-up visit 3 months post-treatment (T3). Participants are grouped according to receiving sham (Tx0) and active iTBS (Tx123) treatment.

Variable	T1: Tx0 (n=6)	T1: Tx123 (n=18)	T2: Tx0 (n=6)	T2: Tx123 (n=18)	T3: Tx0 (n=5)	T3: Tx123 (n=13)
BNT	41 (13.6)	29.7 (20.1)	48.8 (10.3)	35.6 (21.0)	47.6 (9.6)	28.1 (23.5)
SFT	25.5 (8.9)*	12.8 (10.3)*	29.2 (9.6)	14.6 (11.2)	30.4 (5.3)	13.6 (11.8)
COWAT	9.3 (5.7)	7.2 (6.4)	10.2 (5.6)	8.7 (7.9)	12.6 (5.5)	7 (7.1)
Complex ideation	8.5 (4.4)	6.7 (2.8)	9.2 (3.8)	6.5 (3.5)	9.8 (3.8)	6.8 (3.3)
PPVT	188 (24.2)	184 (25.6) ^a	184.2 (15.6)	185.8 (29.6) ^a	199 (9.5)	175.6 (35.0)
WAB-R Aphasia Quotient*	83.1 (12.6)*	58.4 (29.7) ^{a,*}	80.1 (12.4) ^a	57.9 (30.8) ^c	84.4 (11.1)	61.5 (33.1)
WAB-R Apraxia Total [#]	57 (2.8) [#]	50.9 (11.7) ^{a,#}	57.2 (3.3) ^a	50.3 (11.6) ^c	59.2 (0.8)	52.7 (9.2)
Mini-CAL	55.3 (17.0) ^b	42.5 (10.8) ^e	50 (7.0) ^b	47.8 (16.4) ^e	49.7 (14.0) ^b	53.2 (12.9) ^c
fMRI Verb Generation Task						
Correct trials for "say verbs" [#]	2.4 (2.1) ^{a,#}	0.4 (1.1) ^{d,#}	3.4 (4.5) ^a	0.6 (1.4) ^d	4 (4.2) ^a	2.1 (3.5) ^e
Non-verb words for "say verbs"	18 (12.9) ^a	8.7 (7.1) ^d	14.4 (15.5) ^a	12.1 (9.2) ^d	15 (16.1) ^a	13.5 (11.6) ^e
Correct trials for "repeat nouns" ^{****}	12.8 (1.6) ^{a,****}	5.2 (5.2) ^{d,****}	13 (2.1) ^a	7 (5.6) ^d	14 (1.4) ^a	7.9 (4.7) ^e
fMRI Verbal Paired Associates Task						
Correct trials for "read" ^{**}	26.5 (4.7) ^{b,**}	12.8 (11.3) ^{f,**}	27.6 (3.8) ^a	19 (11.3) [§]	27.2 (4.7)	12.4 (12.9) ^c
Correct trials for "generate" [#]	11.3 (4.4) ^{b,#}	5.4 (6.7) ^{f,#}	14.2 (5.0) ^a	9.3 (8.5) [§]	15.4 (8.1)	7.2 (8.9) ^c
Post-scan Recognition Memory						
Correct memory for "read" ^{**}	20.8 (4.5) ^{a,*}	14.1(6.5) ^{b,*}	22.3 (5.2)	15.4 (7.1) ^b	17.4 (12.3)	18.7 (7.9)
Correct memory for "generate" ^{**}	20.8 (5.2) ^{a,*}	12.4 (7.0) ^{b,*}	20 (5.3)	13.6 (6.8) ^b	17.4 (12.3)	15.6 (6.8)

Scores reported as mean (SD) for each variable. Tx0 and Tx123 groups compared at baseline using 2-sample t-tests. * $P < 0.05$; ** $P < 0.005$; *** $P < 0.001$; # $0.05 \leq P < 0.10$. ^a Missing data for 1 subject; ^b missing data for 2 subject; ^c missing data for 3 subjects; ^d missing data for 4 subjects; ^e missing data for 5 subjects; ^f missing data for 6 subjects; [§] missing data for 7 subjects.

had to generate the second word out loud. After the scan, participants were presented with the target word (eg, "tree" from "bee-t****") along with 2 foils (eg, "bush" and "grass") to assess recognition memory.

MRI Data Acquisition

Neuroimaging was performed using a 3.0 Tesla MRI system. At UC, 3 participants were scanned on a Philips Achieva scanner (Philips Medical Systems, Eindhoven, Netherlands) to acquire

T2*-weighted fMRI scans while performing the VGT and VPAT (TR/TE=2000/38 ms, FOV=24.0×24.0 cm, matrix=64×64, 32 axial 4-mm-thick slices) and T1-weighted anatomical scan (TR/TE=8.1/3.7 ms, FOV 25.0×21.1×18.0 cm, matrix 252×211, flip angle 8°, 1-mm slices). At UAB, 14 participants were scanned on a Siemens Allegra scanner, and after scanner upgrade, 7 participants were scanned on a Siemens Prisma scanner (Siemens Medical Solutions, Erlangen, Germany) to acquire T2*-weighted fMRI scans while performing the VGT and VPAT (TR/TE=2000/38 ms, FOV=24.0×24.0 cm, matrix=64×64, 32 axial 4-mm slices);

after scanner upgrade, TR/TE=2000/35 ms, FOV=24.0×24.0 cm, matrix=64×64, 32 axial 4-mm slices) and T1-weighted anatomical scan (TR/TE=2300/2.17 ms, FOV 25.6×25.6×19.2 cm, matrix 256×256, flip angle 9°, 1-mm-thick slices; after scanner upgrade, TR/TE=2300/3.37 ms, FOV 25.6×25.6×19.2 cm, matrix 256×256, flip angle 9°, 1-mm slices). Participants were fitted with an MRI-compatible headset, response device in their left hand, and an emergency squeeze bulb. A mirror/screen system was positioned for viewing visual stimuli. Once participants were positioned in the scanner, a localizer scan was performed followed by anatomical and fMRI scans.

Functional MRI Data Processing

AFNI software was used MRI analysis [31], including anatomical-fMRI scan alignment and motion correction [32]. Each participant's lesion probability map was created, [33] and used to infill anatomical scan lesions to improve normalization into Montreal Neurologic Institute (MNI) space and create composite lesion maps (Figure 1B). Spatial smoothing of 6-mm Gaussian full-width half-maximum was performed for fMRI scans. Statistical modeling of BOLD response for event types in each task was performed at the single-subject level, while accounting for signal drift and head motion. For the VGT, general linear modeling (GLM) was performed to contrast "say verbs" vs "think verbs" (isolate activation related to speech production/auditory processing) and contrast "say verbs" vs "repeat nouns" (isolate activation related to semantic processing). For the VPAT, GLM was performed to contrast "generate" and "read" conditions (isolate activation related to word generation and encoding).

Statistical Analyses

Participant characteristics and performance were analyzed using SAS, version 9.4 (Cary, NC), and $P < 0.05$ was considered significant. Two-sample t-tests assessed baseline differences between Tx0 and Tx123. Fisher's exact tests were performed to assess baseline group differences in categorical variables (ie, sex and handedness). The Shapiro-Wilk test for normality was performed for the change between time points (T2-T1, T3-T2, and T3-T1) for each behavioral measure for each group. Paired t-tests were performed to assess changes in normally-distributed measures, while the Sign test was performed for measures that did not meet the conditions of normality to examine immediate post-treatment changes induced by sham or iTBS (T2-T1), residual effects after 3 months (T3-T2), or if there were delayed effects after 3 months (T3-T1). Missing data at various time points (Table 2) affected sample size for each paired comparison. Significance thresholds for paired comparisons were $P < 0.05$ (uncorrected), and $P < 0.0167$ after Bonferroni correction for multiple comparisons.

AFNI software was used for MRI statistical analyses [31]. Immediate changes (T2-T1) in fMRI contrasts for each group were assessed using whole-brain paired-samples t-tests, which was the primary study aim. T3-T2 and T3-T1 changes for each group were also performed using paired-samples t-tests to examine 3-month post-treatment effects, and response sustainability or potentially delayed treatment effects after 3 months. The *3dFWHx* program estimated smoothness of noise and fit a mixed model and then the *3dClustSim* program determined the number of voxels/cluster necessary for different thresholds [34]. Monte Carlo simulations ($n=10,000$) calculated cluster thresholds for voxelwise $P=0.05$ necessary to achieve significant activation clusters at corrected $P < 0.05$.

Associations Between fMRI Activation Changes and Performance Changes

Brain and behavior relationships were explored for each significant time-dependent change in fMRI activation in the Tx123 group (T2-T1, T3-T2, and T3-T1) for each task. The average signal for each cluster showing significant changes was extracted from each participant. The change in signal was then correlated with change in behavioral performance for assessments that showed significant changes in the Tx123 group at the corresponding time points. Finally, to replicate previous open-label study results of language therapy primed with left hemisphere iTBS in post-stroke aphasia, an exploratory correlation analysis was performed in the current RCT design using a functionally-defined a priori region of interest in which there was a significant negative correlation between T3-T2 VPAT activation changes in bilateral supplementary motor area (SMA) and AQ change [11]. Thus, in the current study the change in signal from T2 to T3 in the functionally-defined SMA region of interest was correlated with change in AQ between time points showing significant improvements. SAS version 9.4 (Cary, NC) was utilized for Spearman correlation analyses, with $P < 0.05$ considered significant and Bonferroni correction for multiple comparisons as appropriate.

Results

Baseline Group Characteristics

Tx0 and Tx123 did not significantly differ in the proportions of males and females or those who are right-/left-handed, age at MRI scan, years since stroke, and baseline Token Test scores (Table 1). At baseline, Tx0 performed better than Tx123 on the SFT ($P=0.016$), AQ ($P=0.011$), number of correct trials for VGT "repeat nouns" ($P < 0.001$), number of correct trials for the VPAT "read" condition ($P=0.005$), and number of correctly remembered words for "read" ($P=0.028$) and "generate" ($P=0.018$) conditions on the post-scan memory test (Table 2). Tx0 and

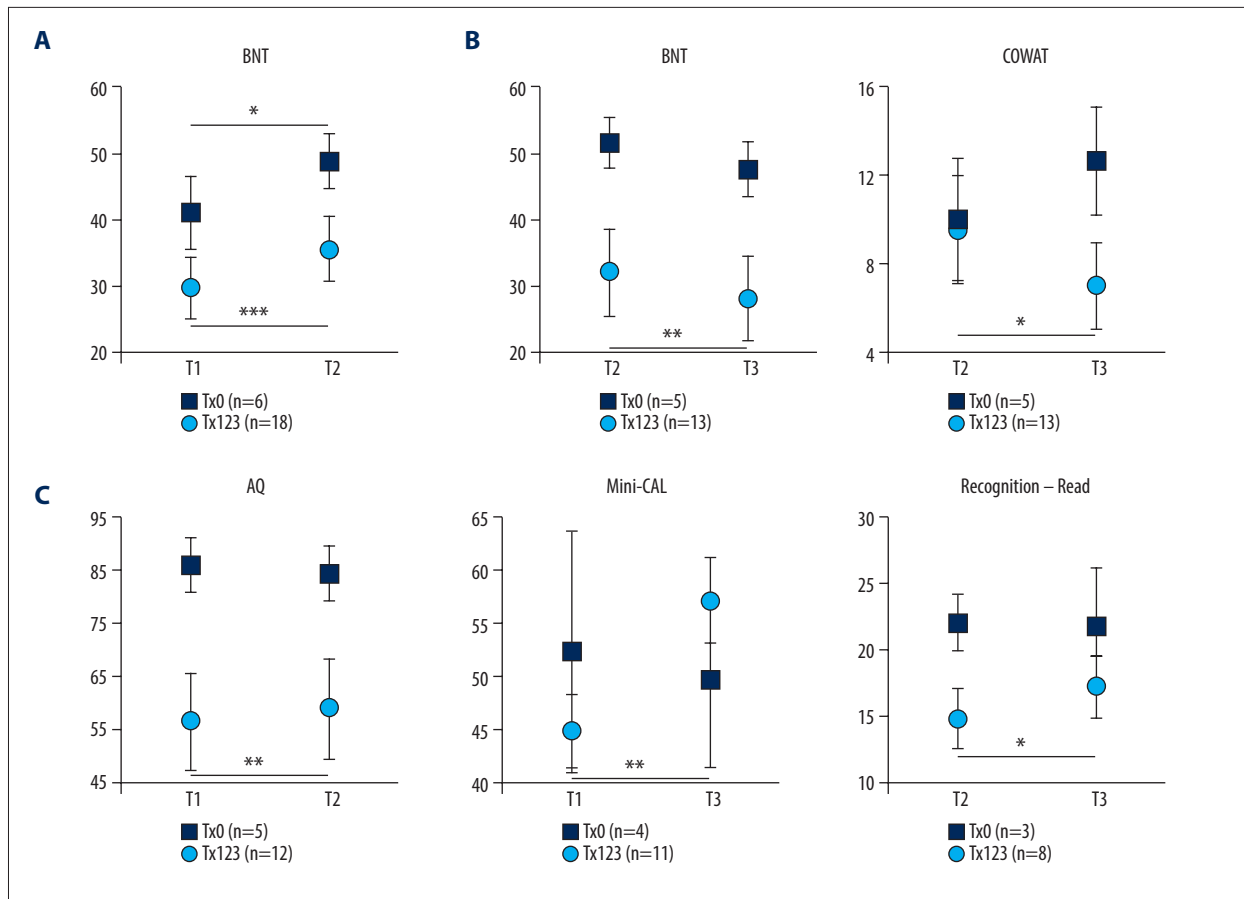


Figure 2. Assessments showing significant changes over time for the treatment groups between the 3 fMRI visits: (A) between baseline (T1) and immediately after treatment (T2); (B) between T2 and at 3-month follow-up (T3); (C) between T1 and T3. Mean \pm SEM are indicated on the graphs, with the line at top part of graph indicates a significant difference between time points for Tx0, while the line at bottom part of graph indicates a significant difference between time points for Tx123. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Tx0 – 3 weeks sham; Tx123 – at least 1 week of iTBS; BNT – Boston Naming Test; COWAT – Controlled Oral Word Association Test; AQ – Aphasia Quotient score on the Western Aphasia Battery-Revised; Mini-CAL – mini-Communicative Activity Log; Recognition – read – number of correctly remembered words from the “read” condition of the verbal paired associates task.

Tx123 did not significantly differ in performance for other baseline assessments, although there was a trend of better Tx0 performance on the WAB-R Apraxia Total ($P=0.059$), the number of correct trials for VGT “say verbs” ($P=0.092$), and number of correct trials for the VPAT “generate” condition ($P=0.082$).

Changes in Behavioral Performance

Performance and number of participants with missing data at each visit for each group are summarized in **Table 2**. Between T1 and T2 (**Figure 2A**), Tx0 showed improvement for the BNT ($P=0.010$; $n=6$) and number of correctly remembered words from the VPAT “read” condition ($P=0.041$; $n=5$), and Tx123 showed improvement for BNT ($P < 0.001$; $n=18$), AQ ($P=0.036$; $n=14$), and Apraxia Total ($P=0.031$; $n=14$). Only improvements in BNT for Tx0 and Tx123 remained significant at $P < 0.0167$

after Bonferroni correction. Between T2 and T3 (**Figure 2B**), Tx123 showed decline for BNT ($P=0.0011$; $n=13$) and COWAT ($P=0.012$; $n=13$), which are both significant at $P < 0.0167$ after Bonferroni correction. Between T1 and T3 (**Figure 2C**), Tx123 showed improvement for AQ ($P=0.0011$; $n=12$), mini-CAL ($P=0.0098$; $n=11$) and number of correctly remembered words from the VPAT “read” condition ($P=0.011$; $n=8$), all of which are significant at $P < 0.0167$ after Bonferroni correction.

Changes in Overt Language fMRI Activation

There were significant changes in fMRI task activation between time points for each group (**Figure 3A-3G**, **Table 3**). There was greater VGT activation for speech production/auditory processing at T1 relative to T2 for Tx0 in the bilateral visual cortex (**Figure 3A**) and for Tx123 in the right putamen, insula, superior

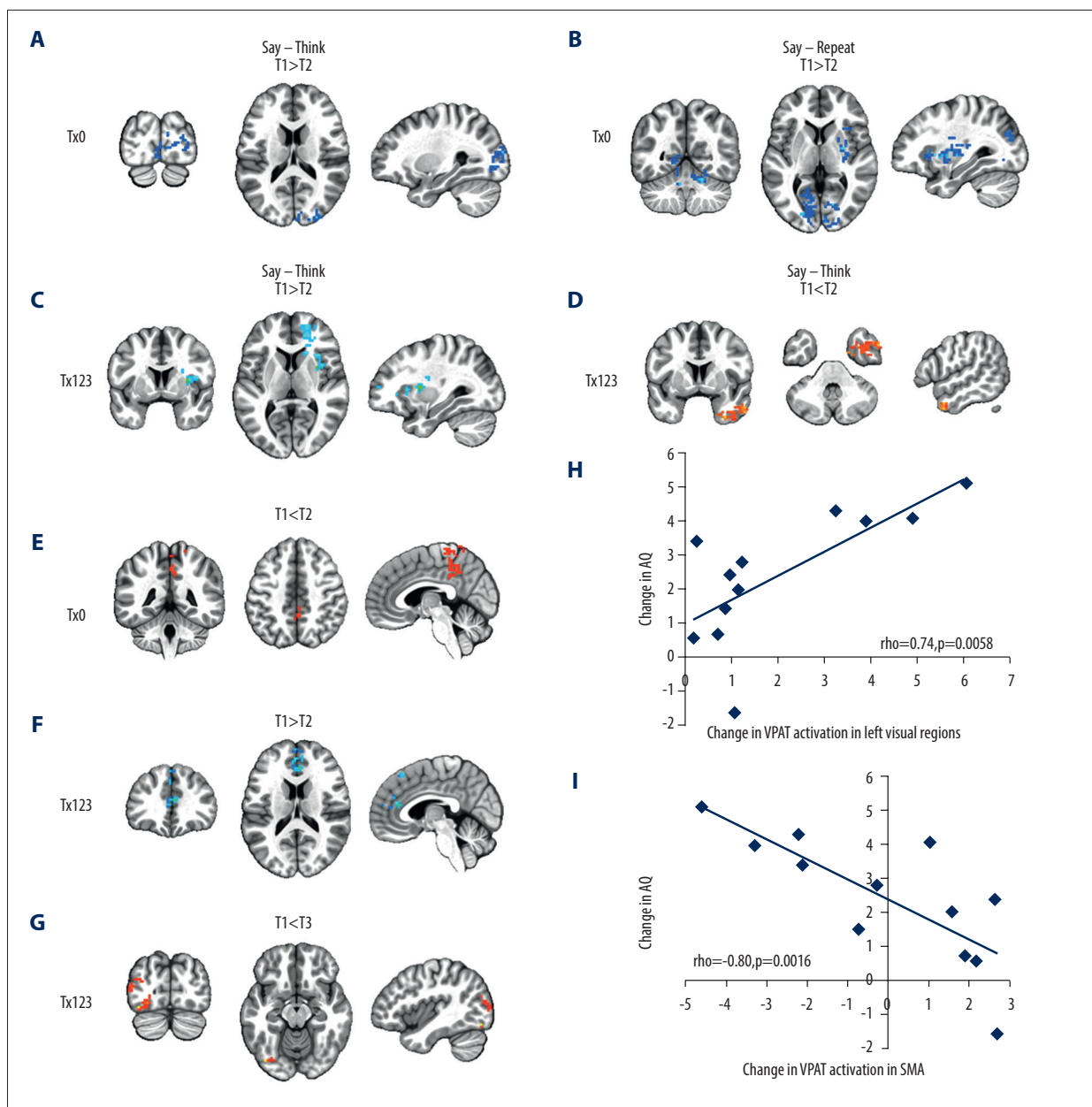


Figure 3. Statistical maps illustrating fMRI activation changes during the verb-generation task (VGT; **A-D**) and verbal paired associates task (VPAT; **E-F**) and scatterplots showing Spearman correlations between changes in VPAT verbal encoding activation and change in aphasia quotient (AQ; **H-I**). Activation clusters are significant at corrected $P < 0.05$. In the coronal (**left image**) and axial (**middle image**) slices, left in the image is left in the brain. Left in the sagittal slice (**right image**) is the anterior part of the brain. (**A**) At T1 compared to T2, Tx0 exhibited greater activation for speech production/auditory processing in the right and extending to the left visual cortex, and (**B**) for noun-verb semantic associations in the right and left visual cortex, right putamen and anterior insula, and bilateral cerebellum. (**C**) Tx123 exhibited greater activation for speech production/auditory processing in the right putamen, insula, superior medial gyrus and anterior cingulate cortex at T1 compared to T2, and (**D**) in the right inferior temporal gyrus at T3 compared to T2. (**E**) Activation for verbal encoding for Tx0 was greater at T2 relative to T1 in the right precuneus, middle cingulate cortex, paracentral lobule and postcentral gyrus. (**F**) Activation for verbal encoding for Tx123 was greater at T1 relative to T2 in the bilateral anterior cingulate cortex, and (**G**) greater at T3 relative to T1 in left visual regions (ie, fusiform gyrus extending to inferior/middle occipital gyrus). (**H**) There was a positive association between change from T1 to T3 in VPAT verbal encoding activation in left visual regions shown in G and corresponding change in AQ. (**I**) There was a negative association between change from T2 to T3 in verbal encoding activation in the a priori region of interest in the bilateral supplementary motor area (SMA) and change in AQ from T1 to T3.

Table 3. Location and cluster extent of brain regions showing significant differences in fMRI activation patterns between time points (T1, T2, T3) for the verb-generation task (VGT) and verbal paired associates task (VPAT). Peak Montreal Neurologic Institute (MNI) coordinates (x, y, z) and t-value for each brain region are also provided.

Contrast	Group	Brain regions	Peak MNI coordinates	Peak t-value	Cluster size (mm ³)
VGT: Speech Production/Auditory Processing (“Say Verbs” vs “Think Verbs”)ª					
T1 >T2	Tx0	R. Middle Occipital Gyrus extending to R. Fusiform Gyrus, and to L. Calcarine Gyrus and Lingual Gyrus	+28, -95, +16	-9.63	4779
	Tx123	R. Putamen extending to R. Insula, Superior Medial Gyrus, and Anterior Cingulate Cortex	+31, +4, +7	-4.31	6102
T2 <T3	Tx123	R. Inferior Temporal Gyrus	+55, +4, -38	4.44	4050
VGT: Processing Noun-Verb Semantic Associations (“Say Verbs” vs “Repeat Nouns”)ª					
T1 >T2	Tx0	R. Calcarine Gyrus extending to L. Cuneus and Middle Occipital Gyrus, and to L. Lingual Gyrus and Superior Occipital Gyrus	+16, -74, +4	-7.88	10,881
		R. Putamen extending to R. Anterior Insula	+31, +13, +1	-9.30	5373
		R. Cerebellum extending to L. Cerebellum	+19, -56, -23	-7.84	3915
VPAT: Verbal Encoding (“Generate” vs “Read”)ª					
T1 <T2	Tx0	R. Precuneus extending to Middle Cingulate Cortex, Paracentral Lobule, and Postcentral Gyrus	+4, -44, +46	7.62	4239
T1 >T2	Tx123	R./L. Anterior Cingulate Cortex	+4, +34, +16	-4.09	3807
T1 <T3	Tx123	L. Fusiform Gyrus extending to Inferior/Middle Occipital Gyrus	-41, -80, -14	6.31	3807

L – left; R – right. ª For the VGT contrast of “say verbs” vs “think verbs” in Tx0, simulations yielded cluster thresholds of 3699 mm³ for both T1 vs T2 and T1 vs T3, and 3915 mm³ for T2 vs T3. For the VGT contrast in Tx123, simulations yielded cluster thresholds of 3375 mm³ for T1 vs T2, 3618 mm³ for T2 vs T3, and 3564 mm³ for T1 vs T3.

ª For the VGT contrast of “say verbs” vs “repeat nouns” in the Tx0, simulations yielded cluster thresholds of 3213 mm³ for both T1 vs T2 and T1 vs T3, and 3078 mm³ for T2 vs T3. For the VGT in the Tx123 group, simulations yielded cluster extent volume thresholds of 3213 mm³ for T1 vs T2, 3348 mm³ for T2 vs T3, and 3294 mm³ for T1 vs T3.

ª For the VPAT contrast of “generate” vs “read” in the Tx0 group, simulations yielded a critical cluster extent volume thresholds of 3564 mm³ for T1 vs T2, 4374 mm³ for T2 vs T3, and 4698 mm³ for T1 vs T3. For the VPAT contrast in the Tx123 group, simulations yielded cluster thresholds of 3024 mm³ for T1 vs T2, and 3402 mm³ for both T2 vs T3 and T1 vs T3.

medial gyrus and anterior cingulate cortex (Figure 3C). Tx123 also exhibited greater activation for speech production/auditory processing at T3 relative to T2 in the right inferior temporal gyrus (Figure 3D). Tx0 exhibited a greater VGT activation for processing noun-verb semantic associations at T1 relative to T2 in bilateral visual cortex, right putamen and anterior insula, and bilateral cerebellum (Figure 3B). Activation for VPAT verbal encoding for Tx0 was greater at T2 relative to T1 in the right precuneus, middle cingulate cortex, paracentral lobule and postcentral gyrus (Figure 3E), while for Tx123 activation was greater at T1 relative to T2 in bilateral anterior cingulate cortex (Figure 3F). Finally, Tx123 exhibited greater activation for VPAT verbal encoding at T3 relative to T1 in the left fusiform extending to inferior/middle occipital gyrus (Figure 3G).

Relating fMRI activation changes to performance changes

There was no significant correlation between T2-T1 change in BNT performance in Tx123 and corresponding T2-T1 activation changes in VGT speech production/auditory processing. There were no significant relationships between T3-T2 change in BNT and COWAT and corresponding activation changes related to VGT speech production/auditory processing. There was a positive correlation ($\rho=0.74$, $P=0.0058$) between T3-T1 change in AQ and corresponding VPAT fMRI activation change for verbal encoding in the left fusiform extending to inferior/middle occipital gyrus (N=12), and significant at $P<0.017$ after Bonferroni correction (Figure 3H). Exploratory analysis showed a significant negative correlation ($\rho=-0.80$, $P=0.0016$) between T3-T1 change in AQ and VPAT fMRI activation change in SMA for verbal encoding from T2 to T3 (N=12; Figure 3I).

Discussion

Using a randomized, double-blind, sham-controlled design, we investigated the effects of iTBS applied to the residual left hemisphere language-responsive cortex as a stand-alone treatment for post-stroke aphasia and its effects on language-related brain activation patterns. The participants in the current study are a subset of those previously reported in Szaflarski et al (2021) but who also completed 2 previously not reported overt language fMRI tasks (VGT and VPAT) during the same MRI sessions at least at T1 and T2 and performed additional language assessments. We observed improvements in a number of assessments between different time points in the Tx123 that were not observed in Tx0, particularly for the AQ (Figure 2A), post-scan recognition of VPAT “read” words, and mini-CAL (Figure 2C). We further showed that delayed AQ improvement for Tx123 is associated with increased recruitment of fusiform extending to inferior/middle occipital gyrus from baseline to 3 months post-treatment (Figure 3H), and with decreased SMA activation related to VPAT verbal encoding from immediate to 3 months post-treatment (Figure 3I). These changes and relationships all remained significant after correction for multiple comparisons. These findings and how they build upon our understanding of language recovery warrant further discussion.

Language Improvements with iTBS

Consistent with a previous open-label study of language therapy primed with iTBS [6,11] we observed BNT gains for both groups with the gains being more significant for Tx123 than Tx0 (Figure 2A). BNT improvement in this subset was also consistent with previously reported iTBS RCT results [10], although improvements were not sustained given the declines in performance from immediate to 3 months post-treatment for both groups (Figure 2B), which was likely due to the current study's smaller sample sizes. These results suggest that naming improvement may have been partially due to practice effects. However, the greater degree of improvement in Tx123 suggests iTBS did have an enhancing effect on performance, but this effect was not retained. Future neurostimulation RCTs should consider incorporating booster treatments (eg, follow-up sessions of stimulation) after some amount of time following the main intervention to test if the improvements may be maintained or regained. The idea of booster treatments has been applied to motor stroke recovery, have been shown to recoup the majority of initial improvement over a year after the initial therapy [35] and therefore show promise in maintaining beneficial effects of initial treatment [36]. Further, it seems that effects on naming ability may not be specific to iTBS since a previous RCT of language therapy alone for post-stroke aphasia also showed improved naming performance over time [37].

Additionally, from baseline to 3 months post-treatment, Tx123 exhibited delayed improvements on AQ, post-scan recognition of VPAT “read” words, and in perception of communicative ability that were not observed in the sham-treated group. Delayed AQ improvement was previously shown in an open-label study of CIAT primed with iTBS [6,11] and in the results of the primary iTBS RCT [10]. These results support the notion of delayed iTBS effects with respect to improving not only aphasia symptoms but also recognition memory, and these likely contributed to the improved perception of communicative ability, which is consistent with the previous open-label study of CIAT primed with iTBS [11]. Future investigations are needed to assess whether or not these delayed improvements may be maintained and for how long.

fMRI Activation Changes with iTBS

Both groups exhibited VGT activation changes from baseline to immediate post-treatment. Treatment with iTBS resulted in decreased activation related to VGT speech production/auditory processing from baseline to immediate post-treatment in the right prefrontal and anterior insula region (Figure 3C) whereas the sham-treated group showed a decreased right visual region activation (Figure 3A). The sham-treated group also showed baseline to immediately post-treatment activation decreases for verb-generation processing (Figure 3B). Since neither group exhibited significant improvements in performance, decreased activation immediately after treatment for both groups likely reflects decreased neural recruitment to maintain performance, similar to our previous report [11]. However, given group differences in baseline VGT performance and in location of greatest lesion overlap, it is not surprising that activation differences over time involved differing brain regions. The widely distributed and bilateral nature of the language network that includes homologous language regions in the less dominant hemisphere likely explains right frontal activation changes in Tx123 that received iTBS application to left frontal regions [15,38]. The iTBS-treated group did show additional increased right temporal activation from immediate to 3 months post-treatment that was not observed in Tx0, suggesting the potential for iTBS to promote neuroplastic changes at least 3 months after treatment completion.

Both groups exhibited VPAT activation changes from baseline to immediate post-treatment, where the sham-treated group had increased activation in midline motor control regions (Figure 3E), while the iTBS group had decreased activation in midline frontal regions (Figure 3F). The sham-treated group showed a parallel trend of improved performance for the VPAT “generate” condition ($P=0.057$), which is likely reflected by the increased motor activation. On the other hand, the iTBS-treated group showed decreased frontal activation without significant change in in-scanner performance. Similar to the observed VGT pattern, this may indicate decreased neural recruitment to maintain performance. Furthermore, only the iTBS-treated group exhibited significant

change in VPAT activation from baseline to 3 months post-treatment (**Figure 3G**), which further supports a delayed effect of iTBS on brain plasticity. This delayed increase in VPAT activation in the iTBS-treated group parallels delayed improvement in post-scan recognition memory for read words and is likely indicative of more effective memory encoding process with iTBS. There was a similar pattern of delayed fMRI activation changes observed in the larger group of participants that completed the main study fMRI tasks of semantic-/tone-decision making and was previously described [10]. Together these results lend itself to the notion that neuroplastic and language function changes induced by iTBS may not be immediate, but rather that iTBS may have a delayed effect and underscores the importance of having a follow-up period after treatment completion.

fMRI Activation Changes Underlying Language Improvements

The delayed increase from baseline to 3 months post-treatment in VPAT fMRI activation for verbal encoding in the left visual cortex (ie, fusiform extending to inferior/middle occipital gyrus), which encompass part of the ventral visual stream [39] was significantly correlated with the corresponding delayed improvement in aphasia symptoms in the iTBS-treated group ($\rho=0.74$, $P=0.0058$; **Figure 3H**). Visual processing is involved and necessary for language function during VPAT fMRI given that the pairs of words are visually presented. Further, the visual word form area that includes left fusiform gyrus is related to processing written language and is strongly activated to reading words [38], which are a required part of task performance on the VPAT. While in-scanner performance improvement for the VPAT was not observed in the iTBS-treated group, they did exhibit a delay in post-scan recognition memory improvement as stated above. Ventral and dorsal visual streams were shown to play an important role in word retrieval for video naming compared to picture naming [40], with ventral stream involvement in object representation and recognition [41,42]. A recent study of augmentative and alternative communication also postulated that the weakened spoken language system in aphasia may be enhanced by a more intact visual system [43]. Our findings provide additional support for the coupling of the visual and language systems to promote improved language function in post-stroke aphasia.

Further, decreased VPAT activation from immediate to 3 months post-treatment in the functionally-defined SMA region of interest was correlated with delayed aphasia symptom improvement ($\rho=-0.80$, $P=0.0016$; **Figure 3I**). This negative correlation aligns with the effects observed in our previous open-label study of language therapy primed with iTBS that showed the same effect [11] and suggests iTBS promotes more efficient processing in the SMA with improved language function in those with post-stroke aphasia. The SMA controls functions

during language processing in addition to its involvement in speech motor control [44]. SMA syndrome in which patients suffer from both motor and speech/language dysfunction is a common complication associated with dorsomedial prefrontal lesions and surgery [45,46]. Language deficits including impaired word retrieval have been linked to the disruption of the left frontal aslant tract primarily connecting the SMA to IFG in the left hemisphere [38,45,47-49]. Thus, the current results further support a role for decreased SMA activity during language processing in the iTBS-induced delayed improvements in aphasia symptoms. Overall, our study suggests that iTBS alone may induce slower changes in neural substrates involved in visual processing and motor function as part of a more widely distributed language network [38], and that are associated with delayed treatment gains in language function.

Study Limitations

The limitations to the current study should be considered for future neurostimulation rehabilitation studies in post-stroke aphasia. Recruitment and retention of participants in longitudinal randomized rehabilitation trials are challenging, which contributed to the missing data, particularly at 3 months post-treatment. This limited our ability to interpret effects of iTBS on those specific data where sample size for paired comparisons between time points was reduced. The small number of participants completing longitudinal follow-up and the amount of missing data also necessitated combining the iTBS treatment groups, which did not allow us to investigate dose-dependent behavioral and fMRI changes. It should also be noted that the 2 groups differed at baseline, with Tx0 performing significantly better than Tx123 on a number of assessments and limits some of the interpretations of our results. This is likely due to the small sample size of each arm, and future RCT studies with larger sample sizes would allow for the randomization procedure to be more effective. Finally, blinding of both the participant and the study team members who took the participant through the study procedures (eg, language assessments and MRI) and analyzed the data was an important component of the study, and it is possible that participants were aware of which treatment arm they were in. We did not ask whether they could discern if they were receiving sham versus iTBS treatment, but participants could be surveyed in future studies to assess effectiveness of the blinding procedures.

Conclusions

The observed iTBS-induced language improvements and associations between delayed fMRI activation changes and aphasia symptom improvement support the therapeutic and neurorehabilitative potential of stand-alone iTBS in chronic post-stroke aphasia recovery and the need for further investigation of its effects.

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References:

- Hilari K, Needle JJ, Harrison KL. What are the important factors in health-related quality of life for people with aphasia? A systematic review. *Arch Phys Med Rehabil.* 2012;93:S86-95
- Lazar RM, Boehme AK. Aphasia as a predictor of stroke outcome. *Curr Neurol Neurosci Rep.* 2017;17:83
- Zumbansen A, Thiel A. Recent advances in the treatment of post-stroke aphasia. *Neural Regen Res.* 2014;9:703-6
- Fridriksson J, Hubbard HI, Hudspeth SG. Transcranial brain stimulation to treat aphasia: A clinical perspective. *Semin Speech Lang.* 2012;33:188-202
- REhabilitation and recovery of people with Aphasia after Stroke (RELEASE) Collaborators. Predictors of poststroke aphasia recovery: A systematic review-informed individual participant data meta-analysis. *Stroke.* 2021;52:1778-87
- Szaflarski JP, Griffis J, Vannest J, et al. A feasibility study of combined intermittent theta burst stimulation and modified constraint-induced aphasia therapy in chronic post-stroke aphasia. *Restor Neurol Neurosci.* 2018;36:503-18
- Szaflarski JP, Vannest J, Wu SW, et al. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. *Med Sci Monit.* 2011;17:CR132-39
- Harvey DY, Podell J, Turkeltaub PE, et al. Functional reorganization of right prefrontal cortex underlies sustained naming improvements in chronic aphasia via repetitive transcranial magnetic stimulation. *Cogn Behav Neurol.* 2017;30:133-44
- Haghighi M, Mazdeh M, Ranjbar N, et al. Further evidence of the positive influence of repetitive transcranial magnetic stimulation on speech and language in patients with aphasia after stroke: Results from a double-blind intervention with sham condition. *Neuropsychobiology.* 2017;75:185-92
- Szaflarski JP, Nenert R, Allendorfer JB, et al. Intermittent theta burst stimulation (iTBS) for the treatment of chronic post-stroke aphasia: Results of a pilot randomized, double-blind, sham-controlled trial. *Med Sci Monit.* 2021;27:e931468
- Allendorfer JB, Nenert R, Nair S, et al. Functional magnetic resonance imaging of language following constraint-induced aphasia therapy primed with intermittent theta burst stimulation in 13 patients with post-stroke aphasia. *Med Sci Monit.* 2021;27:e930100
- Shah PP, Szaflarski JP, Allendorfer J, et al. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. *Front Hum Neurosci.* 2013;7:888
- Mottaghy FM, Hungs M, Brugmann M, et al. Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology.* 1999;53:1806-12
- Finocchiaro C, Maimone M, Brighina F, et al. A case study of primary progressive aphasia: Improvement on verbs after rTMS treatment. *Neurocase.* 2006;12:317-21
- Griffis JC, Nenert R, Allendorfer JB, et al. The canonical semantic network supports residual language function in chronic post-stroke aphasia. *Hum Brain Mapp.* 2017;38:1636-58
- Gamboia OL, Antal A, Moliadze V, et al. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Exp Brain Res.* 2010;204:181-87
- Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. *Neuron.* 2005;45:201-6
- De Renzi E, Vignolo LA. The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain.* 1962;85:665-78
- Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test.* Second ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001
- Lezak M. *Neuropsychological assessment.* New York: Oxford University Press; 1995
- Kozora E, Cullum CM. Generative naming in normal aging – total output and qualitative changes using phonemic and semantic constraints. *Clinical Neuropsychologist.* 1995;9:313-20
- Kertesz A. *Western aphasia battery – revised.* San Antonio, TX: Psychological Corporation; 2006
- Goodglass H, Kaplan E. *The assessment of aphasia and related disorders.* Philadelphia: Lea & Febiger; 1972
- Dunn L, Dunn M. *Peabody picture vocabulary test.* Fourth ed. Minneapolis, MN: NCS Pearson, Inc.; 2007
- Szaflarski JP, Ball A, Grether S, et al. Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. *Med Sci Monit.* 2008;14:CR243-50
- Schmithorst VJ, Holland SK. Event-related fMRI technique for auditory processing with hemodynamics unrelated to acoustic gradient noise. *Magn Reson Med.* 2004;51:399-402
- Allendorfer JB, Lindsell CJ, Siegel M, et al. Females and males are highly similar in language performance and cortical activation patterns during verb generation. *Cortex.* 2012;48:1218-33
- Vannest J, Eaton KP, Henkel D, et al. Cortical correlates of self-generation in verbal paired associate learning. *Brain Res.* 2012;1437:104-14
- Nair S, Nenert RE, Allendorfer JB, et al. Sex, age, and handedness modulate the neural correlates of active learning. *Front Neurosci.* 2019;13:961
- Siegel M, Allendorfer JB, Lindsell CJ, et al. The effects of linguistic relationships among paired associates on verbal self-generation and recognition memory. *Brain Behav.* 2012;2:789-95
- Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996;29:162-73
- Cox RW, Jesmanowicz A. Real-time 3D image registration for functional MRI. *Magn Reson Med.* 1999;42:1014-18
- Griffis JC, Allendorfer JB, Szaflarski JP. Voxel-based Gaussian naive Bayes classification of ischemic stroke lesions in individual T1-weighted MRI scans. *J Neurosci Methods.* 2015;257:97-108
- Cox RW, Chen G, Glen DR, et al. fMRI clustering in AFNI: False-positive rates redux. *Brain Connect.* 2017;7:152-71
- Rijntjes M, Haevernick K, Barzel A, et al. Repeat therapy for chronic motor stroke: A pilot study for feasibility and efficacy. *Neurorehabil Neural Repair.* 2009;23:275-80
- Morris DM, Taub E, Mark VW, et al. Protocol for a randomized controlled trial of CI therapy for rehabilitation of upper extremity motor deficit: The Bringing Rehabilitation to American Veterans Everywhere Project. *J Head Trauma Rehabil.* 2019;34:268-79
- Nenert R, Allendorfer JB, Martin AM, et al. Neuroimaging correlates of post-stroke aphasia rehabilitation in a pilot randomized trial of constraint-induced aphasia therapy. *Med Sci Monit.* 2017;23:3489-507
- Middlebrooks EH, Yagmurlu K, Szaflarski JP, et al. A contemporary framework of language processing in the human brain in the context of preoperative and intraoperative language mapping. *Neuroradiology.* 2017;59:69-87
- Hickok G, Poeppel D. Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition.* 2004;92:67-99
- den Ouden DB, Fix S, Parrish TB, et al. Argument structure effects in action verb naming in static and dynamic conditions. *J Neurolinguistics.* 2009;22:196-215
- Moore CJ, Price CJ. Three distinct ventral occipitotemporal regions for reading and object naming. *Neuroimage.* 1999;10:181-92

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42. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci.* 1992;15:20-25
43. Dietz A, Vannest J, Maloney T, et al. The feasibility of improving discourse in people with aphasia through AAC: Clinical and functional MRI correlates. *Aphasiology.* 2018;32:693-719
44. Hertrich I, Dietrich S, Ackermann H. The role of the supplementary motor area for speech and language processing. *Neurosci Biobehav Rev.* 2016;68:602-10
45. Pinson H, Van Lerbeirghe J, Vanhauwaert D, et al. The supplementary motor area syndrome: A neurosurgical review. *Neurosurg Rev.* 2021 [Online ahead of print]
46. Yao S, Liebenthal E, Juvekar P, et al. Sex effect on presurgical language mapping in patients with a brain tumor. *Front Neurosci.* 2020;14:4
47. Nakajima R, Kinoshita M, Okita H, et al. Disconnection of posterior part of the frontal aslant tract causes acute phase motor functional deficit. *Brain Cogn.* 2021;151:105752
48. Obayashi S. The supplementary motor area responsible for word retrieval decline after acute thalamic stroke revealed by coupled SPECT and near-infrared spectroscopy. *Brain Sci.* 2020;10:247
49. Catani M, Mesulam MM, Jakobsen E, et al. A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain.* 2013;136:2619-28