Improved Language in a Chronic Nonfluent Aphasia Patient After Treatment With CPAP and TMS

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Abstract:

Objective: To present pretreatment and post-treatment language data for a nonfluent aphasia patient who received 2 treatment modalities: (1) continuous positive airway pressure (CPAP) for his sleep apnea, starting 1-year poststroke; and (2) repetitive transcranial magnetic brain stimulation (TMS), starting 2 years poststroke.

Background: Language data were acquired beyond the spontaneous recovery period of 3 to 6 months poststroke onset. CPAP restores adequate oxygen flow throughout all stages of sleep, and may improve cognition. A series of slow, 1 Hz repetitive TMS treatments to suppress a posterior portion of right pars triangularis has been shown to improve phrase length and naming in chronic nonfluent aphasia.

Method: The Boston Diagnostic Aphasia Examination and Boston Naming Test were administered pre-CPAP, and after 2 to 5 months of CPAP. These same tests were administered pre-TMS, and at 3 and 6 months post-TMS, and again 2.4 years later.

Results: Post-CPAP testing showed increased Phrase Length, Auditory Comprehension, and naming Animals and Tools/Implements (Boston Diagnostic Aphasia Examination). Testing at 3 and 6 months post-TMS showed significant increase in Phrase Length, Auditory Comprehension, and Boston Naming Test compared with pre-TMS. These gains were retained at 2.4 years post-TMS. CPAP use continued throughout.

Conclusions: Physiologic treatment interventions may promote language recovery in chronic aphasia.

Keyword: aphasia | CPAP | TMS | speech | language | stroke rehabilitation

Article:

Each year, there are approximately 80,000 new cases of adult aphasia due to stroke,[1] and 50% to 60% of cases continue to have chronic, communicative impairment.[2,3] Approximately 20% have hesitant, poorly articulated, agrammatic speech with word-finding problems (nonfluent aphasia).[4]

The relative role of neuroplasticity in the right hemisphere (RH), or in the left hemisphere (LH) in aphasia recovery remains unknown. In functional imaging studies with nonfluent aphasia, an increased, possible "overactivation" in RH frontal regions (inferior frontal gyrus, IFG; and motor cortex, M1) has been observed.[5–9] This possible RH overactivation may be related to transcallosal disinhibition from the damaged, dominant LH, leading only to partial, or incomplete recovery.

Heiss and Thiel [10] have suggested that in long-term recovery, RH recruitment may be less efficient than restoring the LH network, where better recovery has been associated with higher activation in left superior temporal gyrus (STG) and left supplementary motor area.[11,12] Recovery of naming has been associated with reperfusion of left Brodmann area (BA) 37, particularly in acute stroke cases studied with perfusion weighted imaging.[13] Winhuisen et al [14] also observed as early as 2 weeks poststroke onset that better performance on a verbal fluency test (and better recovery) was associated with left IFG. After speech-language therapy with some chronic stroke patients, new LH activation has been associated with improvement in language.[15–17] Richter et al [18] have observed therapeutic success after treatment with constraint-induced aphasia therapy to be correlated with relative decrease of activation in RH areas, including the IFG/insular cortex.

In some studies that included a variety of patients with aphasia, RH activation was considered to be compensatory.[19–23] New RH activation has also been observed after speech-language therapy in patients with aphasia.[23–26] Fernandez et al [27] suggested that RH participation in the acute recovery stage of LH stroke may be followed later, by LH activation corresponding to further recovery, and that the RH may play a larger role in supporting recovery when there is greater damage to LH language areas. Whether recovery in aphasia is mediated primarily from the LH, or from RH language homologs (or both), these studies suggest that there is potential for brain reorganization and improved language in poststroke aphasia.[28] The underlying mechanisms remain elusive and there is need for additional treatment programs.

This case report presents language data acquired from 6 months poststroke onset (MPO) to 4.6 years poststroke, for a nonfluent aphasia patient who was treated with 2 physiologic treatment modalities beginning at 12.5 MPO: (1) continuous positive airway pressure (CPAP) to treat his sleep apnea; and (2) repetitive transcranial magnetic brain stimulation (rTMS), previously

reported to improve phrase length and picture naming in patients with chronic nonfluent aphasia.[29–31]

MATERIALS AND METHODS

Participant

The patient was a right-handed man who suffered a left middle cerebral artery embolic stroke at age 43. He received intravenous tissue plasminogen activator for the left middle cerebral artery clot with narrowing of the basilar artery. His history was significant for atrial septal defect that was repaired at age 9 with open heart surgery in Boston. He was born in Venezuela, premature in the seventh month, weighing 2 pounds (his twin died). He considered English his native language, but also spoke fluent Spanish.

There was a residual right hemiparesis. He walked without a leg brace or a cane, and some finger flexion/spasticity was present. He was a graduate of a 2-year junior college and had been a grocery store manager.

Structural Magnetic Resonance Imaging Scan and LH Lesion Sites

At 12 MPO, a 3-dimensional magnetization prepared rapid gradient echo (3D MPRAGE) magnetic resonance imaging (MRI) scan was obtained using a Siemens Vision Symphony/Quantum 1.5T scanner (field of view=256×256, 0.5 mm slice thickness, no gap; in plane resolution, 0.5×0.5 mm) (Figure 1).

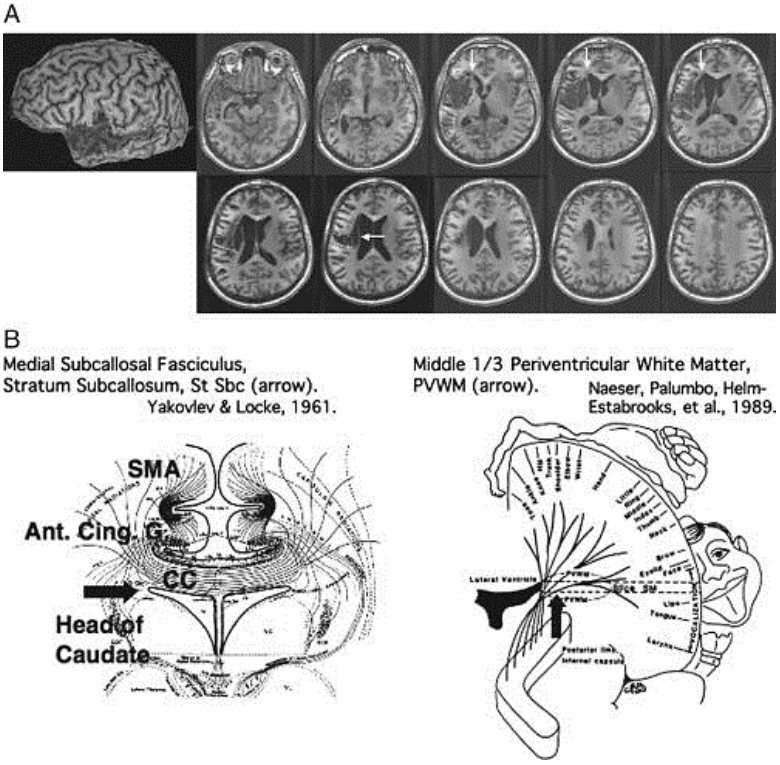

Figure 1. A, Structural MRI scan (3-dimensional magnetization prepared rapid gradient echo) obtained at 1-year poststroke. Large cortical lesion was present in the left temporal lobe, including anterior portions of superior and middle temporal gyrus, with posterior extension across most of the middle temporal gyrus (BA 21). Only small lesion was present in the more anterior portion of Wernicke area. Small cortical lesion was present in only the most inferior portions of Broca area. The lesion was primarily subcortical in the 2 deep white matter areas near ventricle, associated with persistent nonfluent speech: (1) medial subcallosal fasciculus area, deep to Broca area and adjacent to frontal horn (vertical white arrows); and (2) periventricular white matter area adjacent to body of lateral ventricle, deep to sensori-motor mouth area (horizontal white arrow). B, Diagrams showing location, and some pathways within each of these 2 white matter areas adjacent to ventricle: (1) medial subcallosal fasciculus area adjacent to frontal horn, showing pathways from SMA and anterior cingulate gyrus to head of caudate (horizontal black arrow); and (2) periventricular white matter (PVWM) adjacent to body of lateral ventricle (vertical black arrow). Also see the text, where additional pathways are listed. BA indicates Brodmann area; MRI, magnetic resonance imaging; SMA, supplementary motor area.

Most of the cortical lesion was in the left temporal lobe, where lesion included the anterior portion of the STG and middle temporal gyrus (MTG). The STG lesion included only a small, anterior portion of Wernicke area. This lesion was compatible with the potential for some recovery of auditory comprehension.[32,33] Cortical lesion was also present in all of the left MTG (BA 21), including the superior temporal sulcus. In the left frontal lobe, small cortical lesion was present in only the most inferior part of Broca area, and the sensory cortex area. No cortical lesion was present in the left supramarginal or angular gyrus areas. The lesion was primarily subcortical, centered over the putamen, with deep anterior and superior white matter lesion extension, near ventricle. Lesion in these deep white matter areas is associated with persistent nonfluent speech,[34,35] which otherwise would not be expected in a patient with primarily only temporal lobe lesion. These 2 areas are: (1) the medial subcallosal fasciculus (MScF) area, deep to Broca area and located adjacent to the left frontal horn; and (2) the middle one-third periventricular white matter (PVWM) area, deep to the sensorimotor cortex area for mouth and located adjacent to body of caudate and body of the lateral ventricle. The MScF includes pathways from the supplementary motor area and the anterior cingulate gyrus area (BA 24) to head of the caudate, and these fibers may play a role in part, for the initiation of speech output. The PVWM area contains afferent and efferent pathways for mouth (and upper and lower limb), thalamo-cortical, callosal, and occipito-frontal pathways; and these fibers may play a role in part, for motor-sensory aspects of speech production. Because this patient had lesion in less than half of the MScF and lesion in about half of the PVWM, there was potential for recovery of a longer phrase length. The right hemiparesis was likely associated with lesion in the PVWM, because there was no lesion in the posterior limb, internal capsule, or motor cortex. (Due to the presence of metal staples in the sternum, a 3T overt naming functional MRI scan could not be performed.)

Two Treatment Modalities

CPAP

At 6 MPO, when the patient was evaluated by the neurologist (R.K.), he displayed excessive sleepiness and fatigue. Later, after a sleep study, he was diagnosed with obstructive sleep apnea (OSA). CPAP, delivered by face mask throughout the night, has demonstrated benefit for the majority of those with mild to moderate sleep apnea.36 CPAP is continuous, to provide constant pressure, and it is positive, to prevent airway collapse, thus ensuring adequate oxygen flow throughout all stages of sleep.[37] If left untreated, OSA can be associated with higher incidence of hypertension, myocardial arrhythmias, coronary artery, and cerebovascular disease; inadequate sleep has been linked to poor cognitive performance and increased rates of accidents.[38]

The patient began CPAP at 12.5 MPO, which is beyond the 3 to 6-month poststroke time period when most spontaneous recovery has occurred.39 Although CPAP was prescribed for medical reasons, and not planned as a treatment modality for aphasia, some limited language testing was available pre-CPAP at 6 to 8 MPO and at 12 MPO. After 2 to 5 months of CPAP, language testing was performed 3 times (14-17 MPO). The post-CPAP testing was performed as part of baseline language testing before TMS treatment. Language testing included the Boston Diagnostic Aphasia Examination (BDAE) and the Boston Naming Test (BNT).40–42 (Table 1) He had received speech-language therapy only before 12 MPO; not during or after CPAP or TMS.

Table 1. Language Test Scores Pre-CPAP and Post-CPAP and TMS Treatments Boston Diagnostic Aphasia Examination (BDAE, 3rd ed., 2001; and 2nd ed., 1983, Auditory Comprehension Subtests Only) and Boston Naming Test (first 20 pictures)

	Pre-CPAP Testing	Start CPAP		Post-CPAP at 2-5 Mo and pre-TMS Baseline Testing			Pre-TMS Entry Baseline Means and SDs		Start Phase 2 TMS	Post-TMS at 3 and 6 Mo		Post-TMS at 2.4 Y		
				Baseline 1	Baseline 2	Baseline 3			Ten, 20-min. Tx.'s to R PTr, post	3 Mo	6 Mo	29 Mo	29 Mo	29 Mo
Mo Poststroke Onset:	6-8	12	12.5	14	17	17.5			27	30	33	56	56	56
BDAE Subtest (Maximum Possible Score		Score	Score	Score	Score	Score	Mean SD	SD	Mean +2 SD	Score	Score	Score	Score	Score
Spontaneous Speech (Picture Description)														
Articulatory Agility (7)			5	5	5	5	5.00	0.00		5	5	5	5	5
Phrase Length (7)		2-4	2-4	6	4	5	5.00 CPAP	1.00	7.00	11*	7*	6	9*	12*

Grammatical Form (7)		5	5	5	5	5.00	0.00		6	5	5	5	5
Auditory Comprehension (v.2, 1983)													
Word Discrimination (72)	52	60	60	69	70	66.33	CPAP 5.50	77.33	67	65.5	64	69.5	69.5
Body Part I.D. (20)	1210	13.5	12.5	14	13.33	CPAP 1.78	16.89	13	15	16	16	14	
Commands (15)	6	7	11	11	10	10.67	CPAP 1.89	14.45	11	13	11	9	12
Complex Ideational Material (12)		7	5	8	5	6.00	1.50	9.00	6	5	2	4	5
Repetition													
Sentences (10)		1	2	2	2	2.00	0.50	3.00	3*	5*	3*	3*	3*
Naming													
Boston Naming Test (first 20)	8	6	9	8	9	8.67	1.41	11.50	12*	13*	15*	13*	15*
Naming in Categories													
Actions (12)		3	5	4	1	3.33	1.71	6.75	4	5	2	4	3
Animals (12)	5	5	9	6	9	8.00 CPAP	2.06	12.12	7	7	10	9	9
Tools/Implements (12)		2	6	5	6	5.67 CPAP	1.89	9.45	5	2	5	6	6

Results After 2 to 5 Months of CPAP

Post-CPAP, there was improvement in Phrase Length, Auditory Comprehension, and some picture naming (BDAE). On pre-CPAP testing (6-8 MPO and 12 MPO), the longest phrase length on the BDAE cookie theft picture description was 2 to 4 words (eg, “she's cookies”). Post-CPAP, across the 3 testings (14-17 MPO), the mean longest phrase length was 5 words (range, 4-6 words)–for example, at testing one, the longest phrase length was 6 words: “she let it go with water;” at testing two, 4 words: “he got cookie jugs;” and at testing three, 5 words: “gave her and him some.”

An area of major improvement post-CPAP was Auditory Comprehension (Table 1). Pre-CPAP, the Word Discrimination scores were 52 and 60/72; and post-CPAP, the mean across 3 testings was 66.3. For Body Part Identification, pre-CPAP the scores were 12 and 10/20; and post-CPAP, 13.33. For Commands, pre-CPAP, the scores were 6 and 7/15; and post-CPAP, 10.67.

Improvement was also observed post-CPAP on the BDAE subtests for naming Animals, and Tools/Implements. Pre-CPAP, the naming score for Animals was 5/12; and post-CPAP, 8. Pre-CPAP, the naming score for Tools/Implements was 2/12; and post-CPAP, 5.67. It is not possible to know if these changes were significant post-CPAP, due to limited testing, pre-CPAP.

rTMS

As reviewed in the Introduction, functional imaging studies with nonfluent aphasia have observed unusually high, possible "overactivation," in parts of right Broca area and other right perisylvian language homologs during language tasks; this may represent maladaptive plasticity.5–9 Repetitive TMS allows painless, noninvasive stimulation of human cortex (approximately 1 cm3 in size) from outside of the skull. Slow (1 Hz) rTMS decreases excitability in the targeted cortical region of interest (ROI)43,44 that lasts beyond the duration of the train itself,45 leading to measurable behavioral effects. Conversely, rapid rTMS (>=5 Hz) increases cortical excitability.[45]

In our TMS research with chronic nonfluent aphasia patients, we hypothesized that suppression of activity in a targeted RH ROI with slow, 1 Hz rTMS would have an overall modulating effect on functionally connected elements of the distributed neural network for speech and language.29–31 We have observed at 2 months after 10 rTMS treatments applied to right posterior-inferior pars triangularis (PTr), there was significant improvement on 3 naming tests: (1) the BNT, first 20 items (P=0.003); (2) the BDAE subtest, naming Animals (P=0.02); and (3) the BDAE subtest, naming Tools/Implements (P=0.04).31 At 8 months post-rTMS, all 3 naming test scores continued to improve relative to pre-rTMS testing, but only Tools/Implements was significant (P=0.003). None of the 4 patients received any individual speech therapy during or in the 8-month follow-up testing of the TMS study.

rTMS Treatment Protocol in this Case

The patient continued to use CPAP throughout the study (and to date). He signed informed consent forms approved by institutional review boards at all the 3 institutions where this research took place.

Baseline Snodgrass and Vanderwart (S&V) Naming Ability

Before any rTMS, a baseline naming ability for Snodgrass and Vanderwart 46 (S&V) pictures was established. This baseline S&V naming score was later used during phase 1 TMS sessions (explained below) to help establish the best RH cortical ROI to suppress with rTMS, to improve picture naming. During the baseline S&V naming testing, ten, 20-item S&V picture lists were administered across separate testing sessions. His baseline mean S&V naming score was 9.6 (SD=2.67). The TMS treatment protocol consisted of 2 phases.

Phase 1 of TMS

During phase 1 of TMS, a best-response RH cortical ROI was located, which would later become the targeted location for TMS during phase 2. During phase 1, the effect of slow, 1 Hz rTMS for 10 min to suppress activity in each of the 5 different RH frontal regions was examined across separate visits. In this case, the phase 1 visits took place over a 10-month period, due to

scheduling issues. Normally, these visits would take place within a few weeks before the first phase 2 rTMS treatment.

During phase 1, a total of 600 pulses (90% of motor threshold for the left first dorsal interosseus muscle) were delivered to each RH ROI using the Super-Rapid High Frequency MagStim Magnetic Stimulator (MagStim, NY). A figure-8 shaped rTMS coil with a 7 cm outside diameter on each wing was used. This allowed direct stimulation of an area that was about 1×1 cm. The interactive frameless stereotaxic system (Brainsight, Rogue Industries, Montreal) was used with the patient's 3D MPRAGE MRI scan to guide the position of the rTMS coil on the patient's scalp; the coil was held constant across sessions, at approximately 45 degrees. The location of the 5 right frontal ROIs studied during phase 1 are shown in Figure 2. These 5 ROIs included the right M1, mouth (orbicularis oris muscle, as verified with motor evoked potential), and 4 subregions within right Broca area. Each of the 5 RH ROIs was suppressed once, in separate sessions; and later, PTr posterior and PTr middle, were each suppressed again (similar results were obtained).

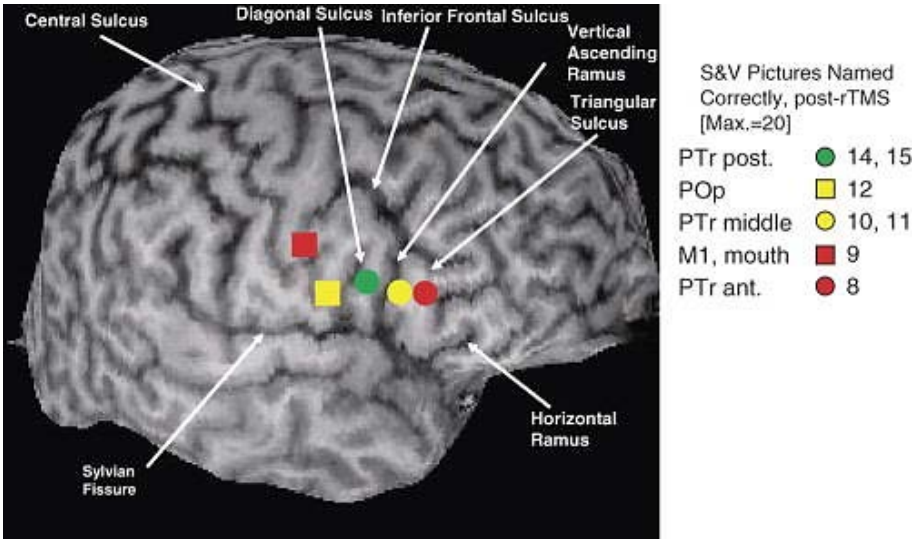

Figure 2. Location of the 5 frontal ROIs that were each suppressed with 1 Hz rTMS for 10 minutes during phase 1 TMS, to determine the best-response ROI. These 5 ROIs included right M1, mouth (orbicularis oris muscle, as verified with MEP), and 4 subregions within right Broca area as defined in the text, using sulcal boundaries (arrows). The gyral location for each ROI that was suppressed with rTMS is marked in color, see legend box. The legend box also shows the number of Snodgrass and Vanderwart (S&V) pictures (max=20) named immediately after rTMS suppression of each ROI. The PTr posterior ROI (green symbol), was the best-response ROI—for example, the area associated with a naming score that reached at least 2 SD above baseline S&V naming ability (eg, 15). 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 2 cm, in a rostral or caudal direction. The PTr posterior ROI (green symbol) was used as the target for suppression with 1 Hz rTMS for ten, 20-minute treatments during phase 2 TMS. M1 indicates motor cortex; MEP, motor evoked potential; POp, pars opercularis; PTr, pars triangularis; ROI, region of interest; rTMS, repetitive transcranial magnetic brain stimulation.

The subregions within right Broca area on the patient's 3D MPRAGE MRI scan were labeled according to sulcal and gyral boundaries as defined by Amunts et al.[47,48] Broca area is classically defined as the pars triangularis (PTr) and pars opercularis (POp) portions of the IFG, and these parts are often considered to correspond in a general manner with the cytoarchitectonic BAs 45 and 44, respectively. We are aware that without cytoarchitectonics, the issue of which anatomic landmark (sulcus) to use as a dividing marker between PTr and POp is not straightforward, especially when a diagonal sulcus (DS) is present, as it was in this case in the RH. When present, the DS is located caudal to the vertical ascending ramus and rostral to the inferior precentral sulcus. When this occurs, an "extra gyrus" within the posterior portion of the IFG is present. Amunts et al [47,48] examined 10 brains (20 hemispheres) both with surface anatomy, and with cytoarchitectonics. They observed large variation across the brains, and when a DS was present (occurring only in every second hemisphere), the DS could either mark the border between BA 45 and 44, or it could be inside BA 44. Thus, without cytoarchitectonics in the present study, it was not possible to know whether the DS was a border between PTr and POp, or if it was within the POp.

Taking the results of Amunts et al [47,48] into consideration for this case study, we arbitrarily chose to use the DS as the dividing marker between the POp and the PTr. The 4 subregions within right Broca area (each about 1 cm apart) were defined as follows: (1) POp: gyrus that is rostral to the inferior precentral sulcus and caudal to the DS; (2) PTr posterior: gyrus that is rostral to the DS and caudal to the vertical ascending ramus; (3) PTr middle: gyrus that is rostral to the vertical ascending ramus and caudal to the triangular sulcus; (4) PTr anterior: gyrus that is rostral to the triangular sulcus and caudal to the horizontal ramus (Figure 2).

Before and after each 10-minute rTMS application to a specific RH ROI, a 20-item S&V set of pictures was presented for the patient to name. The best-response cortical ROI was defined as the ROI that was associated with an S&V naming score, at least 2 SD above the baseline mean S&V naming score. In this case, the S&V naming score after 10 minutes of rTMS to a RH ROI needed to reach at least 15 pictures named correctly (9.6+5.34=14.94), to meet the criterion for best-response RH ROI (baseline mean was 9.6; SD=2.67). The best-response RH ROI in this case was the gyrus located rostral to the DS and caudal to the vertical ascending ramus—for example, right PTr posterior, in Figure 2. Figure 3 shows in bar graphs, the percent change from baseline for S&V pictures named correctly after 10 minutes of rTMS to suppress each of the 5 RH ROIs; the percent change in response time is also shown.

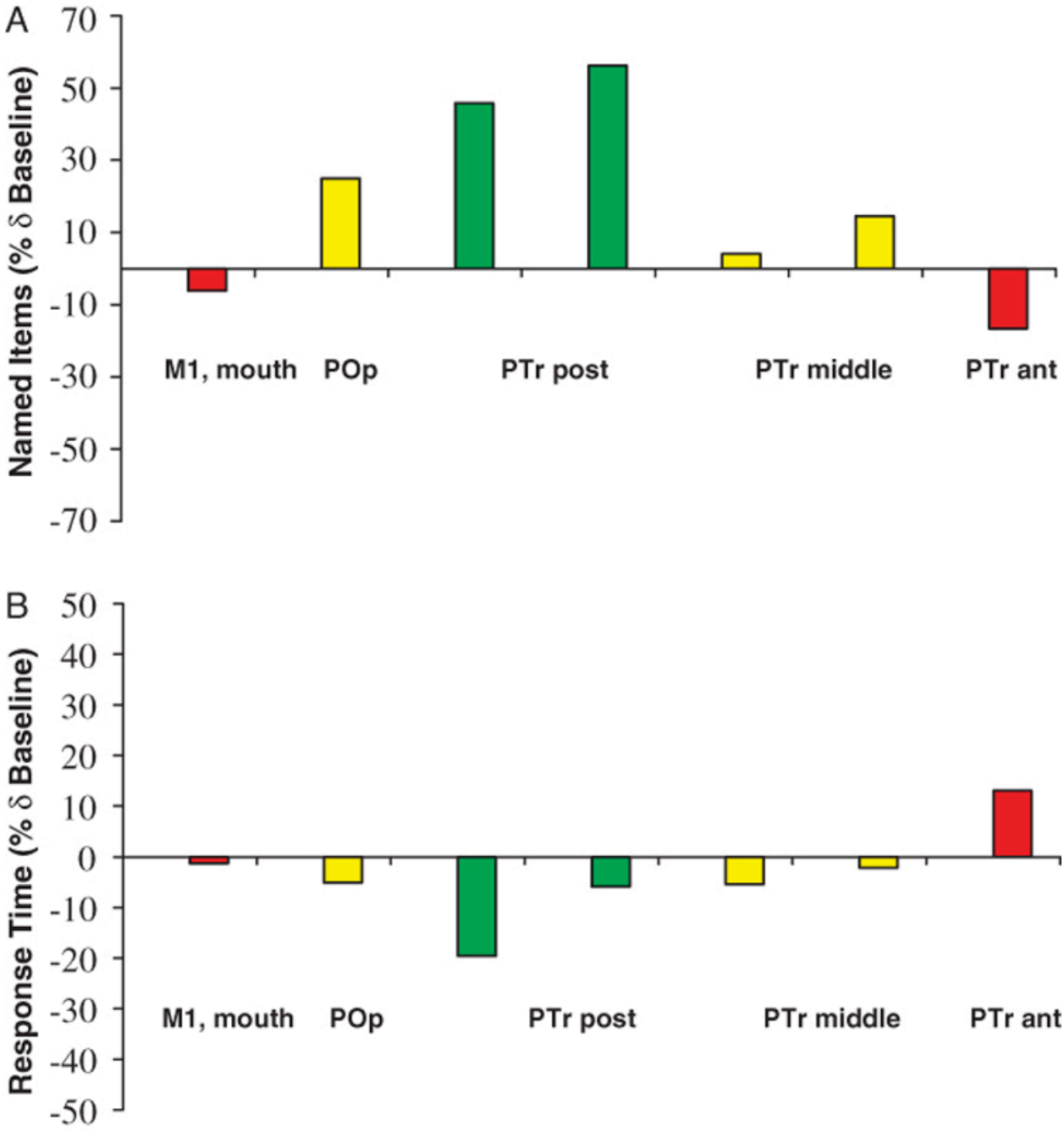

Figure 3. A, Bar graph showing the percent change from baseline, for S&V pictures named correctly after 10 minutes of rTMS to suppress each of the 5 RH ROIs during phase 1 TMS. B, Bar graph showing the percent change from baseline for RT to name the pictures, for each of the 5 RH ROIs. Note, the PTr posterior ROI was associated with the greatest improvement in number of pictures named on 2 occasions. PTr indicates pars triangularis; RH, right hemisphere; ROI, region of interest RT, response time; rTMS, repetitive transcranial magnetic brain stimulation; S&V, Snodgrass and Vanderwart.

Figures 2 and 3 show that when a targeted ROI is located further away from the best-response ROI, naming accuracy decreases. The highest post-rTMS naming scores of 14 and 15 were obtained when right PTr posterior was suppressed (2 separate rTMS sessions). When the coil was positioned 1 cm rostral to the PTr posterior, for example, on the PTr middle, scores of only 10 or 11 were obtained. When the coil was positioned 1 cm caudal to PTr posterior, for example, on the POp, the score of 12 was obtained.

The naming scores were even lower, when the coil was positioned 2 cm rostral to the best-response ROI, for example, on the right PTr anterior (8 pictures named); or 2 cm caudal to best-response ROI, on the M1 mouth (9 pictures named). These scores show that the location of the best-response ROI in this case was precise, for example, the right PTr posterior. These phase 1 data emphasize the importance of testing the effect of rTMS to suppress several ROIs to establish the location of a best-response ROI.

Phase 2 of TMS

During phase 2, the best-response RH ROI from phase 1 was suppressed for a longer treatment time (20 min), and over more days (5 days a wk, for 2 wk). At 27 MPO, this patient received ten, 20-minute rTMS treatments to suppress the right PTr posterior, as shown in Figure 2. On each day of treatment, the rTMS was applied at 1 Hz frequency for 20 minutes (1200 pulses) at 90% of motor threshold (left first dorsal interosseus muscle), as tested each day before treatment. The same equipment used in phase 1, was used in phase 2. Our rTMS parameters are similar to those used in various studies where multiple rTMS treatments were given over time, to help treat depression.49–51 No negative side effects have been reported with these parameters.

Language testing was performed at 3 and 6 months post-phase 2 TMS, and again at 2.4 years later. At the longest time post-TMS, testing was performed 3 times, 4 days apart each time.

Results After TMS Treatments

Significant improvements were observed on Phrase Length for the BDAE cookie theft picture description and naming pictures (BNT) at 3 and 6 months post-phase 2 TMS; these significant gains remained stable at 2.4 years post-TMS. There was also significant improvement on 2 Auditory Comprehension subtests, Body Part Identification and Commands, at 6 months post-rTMS and at 2.4 years (Table 1).

On the BDAE cookie theft picture description, the pre-TMS baseline mean for longest phrase length was 5 words; and at 3 and 6 months post-TMS, it was 11 and 7 words, respectively. The 11-word phrase length at 3 months post-TMS was, “his mother wash the dish up and the water fall down.” At 6 months post-TMS the longest phrase was, “his mother was watching the paper plates.” At 2.4 years post-TMS, the longest phrase length at each of the 3 testing times was 6, 9, and 12 words—for example, 6 words: “the mother was washing some dishes;” 9 words: “water was falling off the sink to the floor;” and 12 words: “she was getting her cookie jars and she

started to fall back." The complexity of his phrases, as well as the length, increased. The BNT score improved from a mean of 8.67 pictures named at baseline to 12 and 13 named at 3 and 6 months post-TMS. These gains in naming were stable at 2.4 years post-TMS, with scores of 15, 13, and 15, at the 3 testing times.

DISCUSSION

This case report documented language improvement after each of the 2 treatment modalities applied later than 1-year poststroke onset, in a patient with nonfluent aphasia. The patient started using the first treatment modality, CPAP, for sleep apnea beginning around 12.5 MPO. After 2 to 5 months of CPAP use, there was improved Phrase Length, Auditory Comprehension, and naming of Animals and Tools/Implements. The patient began treatment with the second modality, TMS, at 27 MPO. At 3 and 6 months as well as at 2.4 years post-TMS, there was significant improvement ($P<0.05$, or 2 SD above pre-TMS baseline mean) in Phrase Length and the BNT. There was significant improvement at 6 months and 2.4 years post-TMS on 2 subtests of BDAE Auditory Comprehension.

Some areas of language improvement post-CPAP and post-TMS were similar, and some were unique to 1 treatment modality. For example, post-CPAP, a major area of improvement was in Auditory Comprehension (Word Discrimination, Body Part Identification, and Commands). Our prior TMS studies with aphasia patients have not observed improvement in Auditory Comprehension testing, post-TMS. In this case, however, there was additional significant improvement in Auditory Comprehension for Body Part Identification and Commands, post-TMS at 6 months and 2.4 years later. Post-CPAP, there were also areas of improvement that overlapped with areas of improvement seen in our previous TMS studies— for example, Phrase Length and naming Animals and Tools/Implements.[29–31]

In addition to improvement in Phrase Length post-TMS, an area of significant improvement that paralleled results from our previous TMS studies was naming pictures on the BNT. At 3 and 6 months post-TMS, this patient had BNT scores of 12 and 13. His baseline mean on this test was 8.67 (SD, 1.41; +2 SD=11.50). This significant gain on the BNT was retained at 2.4 years post-TMS, with scores of 13 to 15.

In this case, there was no additional improvement post-TMS on naming Animals or Tools/Implements, whereas significant improvement in these 2 naming areas had been observed in our previous TMS studies.30,31 There had been improvement in naming Animals and Tools/Implements post-CPAP, however, in this case.

To our knowledge, there are no previous reports on the effect of CPAP on language behavior in stroke patients with aphasia who have sleep apnea. CPAP is a treatment applied for sleep apnea, and although it is not comparable to hyperbaric oxygen treatment in stroke patients (without sleep apnea), they each might have a potential overall effect on cerebral circulation and oxygenation. Sarno et al 52 studied the effect of a single hyperbaric oxygen treatment (100%

oxygen at 2 atmospheres of pressure) on a group of 16 patients with aphasia. There was no significant effect on language, as tested immediately after the 1.5-hour treatment. In contrast, in the present study, CPAP was used almost nightly, for 2 to 5 months, after which, language was again tested.

The specific effect of nightly CPAP use on cortex and brain activation is unknown without functional MRI, which could not be performed in this case. CPAP may have had a more general, overall cortical effect, including improved oxygenation to spared areas of left temporal lobe. Improvement was observed in Auditory Comprehension after CPAP use. This patient spared at least half of the left STG (Wernicke area), which has been associated with potential for improvement in Auditory Comprehension.[32,33]

There was also improvement in naming Animals and Tools/Implements, post-CPAP. Naming ability in these categories has been associated with activation in the mesial occipital cortices and middle infero-temporal areas (animals), and posterior infero-temporal areas and anterior regions of the supramarginal gyrus (tools).[53] This patient had also spared these regions of the left temporo-parietal cortex, and perhaps the repeated use of CPAP mediated some of these temporo-parietal networks associated with naming Animals and Tools/Implements.

The TMS treatments may have been more specific, primarily affecting neural networks associated more with speech output (vs. Auditory Comprehension), including Phrase Length and Naming (BNT). During the 10 rTMS treatments in phase 2, there was suppression of a specific part of right IFG—for example, right PTr posterior. Suppression of this area was hypothesized to reduce the effect of transcallosal disinhibition from the damaged LH on right PTr and thus reducing overactivation of right PTr (and likely exaggerated inhibition of right POp from right PTr posterior, via U-fibers) and in turn, promote better modulation of right POp and the bi-hemispheric neural network for speech and naming.

Components of this neural network in the LH, as reviewed by Gold and Buckner [54] include in part, connections from left inferior prefrontal cortex to left BA 21 (for semantic processing); and connections from left inferior prefrontal cortex to an area near precentral left BA 6 and inferior parietal (left BA 40) (for phonologic processing). Although this patient did have lesion in most of left BA 21 (left MTG), there was no lesion in most of the other components of this neural network in the LH. Thus, whereas speech output did not become entirely normal in this patient post-TMS, there was apparently enough of this neural network remaining that could become active, to enable this patient to have significant improvement in at least 2 subtests requiring speech output—for example, (1) Phrase Length; and (2) the BNT. Post-CPAP, the patient had also shown improvement in aspects of speech output, for example, in Phrase Length, as well as in naming, although specific to BDAE Animals and Tools/Implements, not BNT.

The new, unique improvement post-CPAP had been in Auditory Comprehension, including Word Discrimination, Body Part Identification, and Commands. There was additional,

significant improvement in Body Part Identification and Commands, at 6 months post-TMS, and this was retained at 2.4 years post-TMS. The patient continued to use CPAP, most nights, even out to 2.4 years post-TMS.

The overall positive response for language improvement in this patient after CPAP and TMS is encouraging. The use of both treatment modalities in this case suggests that the neural networks for several aspects of speech and language remain accessible in the chronic stage, poststroke onset. It is likely there are additional physiologic interventions that could access this neuroplasticity.

Another physiologic intervention that holds promise for improvement in patients with chronic aphasia includes transcranial direct current stimulation (tDCS) (cathodal to the left fronto-temporal area).[55] Although the effect of only 1 session was examined, improved naming was observed with an increase of 33.6% (SEM 13.8%) in 8 chronic nonfluent aphasia patients. Multiple tDCS sessions and the long-term language effects have not been reported.

The effect of high-frequency rTMS on naming Actions and Objects in mild and moderate-to-severe Alzheimer disease (AD) has been recently studied.[56] The 20 Hz rTMS was applied to the left or to the right dorsolateral prefrontal cortex areas, for 500 msec while the subject was asked to name a picture on the screen. The mild cases showed significant improvement in naming Actions only; whereas the moderate-to-severe cases showed improvement in naming Actions and Objects. CPAP has been used to treat OSA in patients with AD, where comparison of pretreatment and post-treatment neuropsychologic test scores after 3 weeks of therapeutic CPAP showed significant improvement in cognition.[57]

Results from these studies are similar to the present study, because they suggest a neural plasticity is present in chronic aphasia (and AD). Physiologic intervention with CPAP (when OSA is present), and/or either slow or fast rTMS, or tDCS, when placed on the proper cortical target area with specific treatment parameters, can induce improvement in many aspects of language behavior.

Limitations of this Case Study

Limitations to this case report include: (1) It is unknown if the language improvements post-CPAP alone, were significant, because the patient was only tested twice, before CPAP treatment. (2) It is unknown if the improvement post-CPAP had plateaued after 2 to 5 months of use. The 3 testings over a 3-month period (at 14-17 MPO) after 2 to 5 months of CPAP use suggested stability in the language scores. However, it is not possible to know, if continued use of CPAP alone, and no intervention of TMS, would have yielded the same improvements in language behavior. (3) The relative contribution of rTMS to the significantly improved language scores post-TMS is also unknown, because the patient continued to use the CPAP mask, most nights, throughout the rTMS treatment periods and this continues to date. It is possible there was a synergistic contribution from each intervention, but this also is unknown.

Despite these limitations, results from the present study reinforce results from our previous TMS studies—for example, improvement in Phrase Length, and picture-naming on the BNT after suppression of a posterior portion of right PTr (gyrus located immediately anterior to right POp) with 1 Hz rTMS.29–31 These TMS results also support the notion behind "paradoxical functional facilitation,"[58] where a new, temporary "virtual" lesion (as with 1 Hz rTMS) or a new real lesion (as with a second stroke in a specific location), can improve behavior in chronic stroke. For example, Vuilleumier et al[59] have reported the disappearance of left-sided neglect in a stroke patient with a right parietal infarct, after the appearance of a new left frontal lobe lesion. There are also case studies where ambidextrous adults who had stuttered since childhood no longer stuttered, after unilateral brain damage in adulthood (eg, stroke or head injury), even as soon as 10 days postonset.[60]

Additional studies with single, or multiple physiologic interventions—for example, low-frequency or high-frequency rTMS, tDCS, and even hyperbaric oxygen could all be considered. Recently, transcranial, infrared laser therapy was observed to significantly improve stroke outcome at 90 days (NIH Stroke Severity Scale), when applied once around 18 hours poststroke onset.[61] With the exception of the rTMS protocol presented here (and in our previous TMS papers), these other studies with physiologic interventions have applied only a single session of treatment. It is suggested that more treatment sessions be applied over longer periods of time. Also, the combination of a physiologic intervention with speech therapy sessions provided immediately afterwards, might promote further language improvement in a variety of chronic aphasia patients.

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