Research With Transcranial Magnetic Stimulation in the Treatment of Aphasia

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Repetitive transcranial magnetic stimulation (rTMS) has been used to improve language behavior, including naming, in stroke patients with chronic, nonfluent aphasia. Part 1 of this article reviews functional imaging studies related to language recovery in aphasia. Part 2 reviews the rationale for using rTMS to treat nonfluent aphasia (based on functional imaging) and presents our current rTMS protocol. We present language results from our rTMS studies as well as imaging results from overt naming functional MRI scans obtained before and after a series of rTMS treatments. Part 3 presents results from a pilot study in which rTMS treatments were followed immediately by constraint-induced language therapy. Part 4 reviews our diffusion tensor imaging study examining the possible connectivity of the arcuate fasciculus to different parts of Broca's area (pars triangularis, pars opercularis) and to the ventral premotor cortex. The potential role of mirror neurons in the right pars opercularis and ventral premotor cortex in aphasia recovery is discussed.

Introduction

Electrical stimulation techniques including transcranial magnetic stimulation (TMS) have examined brain–behavior relationships across many cognitive domains (eg, attention, neglect, motor and language systems). TMS can be used to temporarily facilitate or inhibit neural activity to examine intact systems, examine the presence of residual capacity in an injured system, or accelerate natural recovery mechanisms.

We review how TMS has been applied to help reorganize neural networks during language recovery in aphasia. There are four parts: Part 1 reviews functional imaging studies related to recovery of language in aphasia. Part 2 reviews the rationale for use of repetitive TMS (rTMS) in treating nonfluent aphasia based on results from functional imaging studies and reviews our current rTMS treatment protocol with nonfluent aphasia patients. We present language results from our rTMS studies with nonfluent aphasia patients as well as imaging results from overt naming functional MRI (fMRI) scans obtained before and after a series of TMS treatments. Part 3 presents results from a pilot study in which rTMS treatments were followed immediately by constraint-induced language therapy. Part 4 reviews our diffusion tensor imaging (DTI) study examining the possible connectivity of the arcuate fasciculus (AF) to different parts of Broca's area (pars triangularis [PTr], pars opercularis [POp]) and to the ventral premotor cortex (vPMC). Part 4 also addresses the potential role of mirror neurons in the right (R) POp and vPMC in relation to our rTMS results with nonfluent aphasia patients, and in aphasia recovery.

Part 1. Functional Imaging Studies With Aphasia Patients

Brain reorganization supporting recovery of language in aphasia is unclear. Both the left hemisphere (LH) and the right hemisphere (RH) are thought to support language recovery after stroke [1•,2,3]. Factors including time post-stroke when patients are studied (acute or chronic), lesion location, and the specific language tasks examined may affect the mechanisms involved in recovery [3,4]. The most rapid recovery occurs the first 6 months after stroke onset. Approximately 20% of stroke patients have speech and language problems, including hesitant, poorly articulated, agrammatic speech with word-finding problems (nonfluent aphasia) [5]. When functional imaging studies have focused on patients with nonfluent aphasia, an increased activation in RH language homologues has often been observed [6–8,9••].

The LH may be important for better language recovery after stroke [7,8,9••,10–12]. Heiss and Thiel [13] have suggested that for long-term recovery, RH recruitment may be less efficient than LH network restoration. Patients with better recovery were observed to have higher activation in the left (L) superior temporal gyrus (STG) and L supplementary motor area (SMA) [11,14].

Recovery of naming was associated with reperfusion of L Brodmann area (BA) 37 in acute stroke cases studied with perfusion-weighted imaging [15]. Winhuisen et al. [16] also observed, as early as 2 weeks after stroke onset, that better performance on a verbal fluency test (and better recovery) was associated with the L inferior frontal gyrus (IFG). Constraint-induced language therapy (CILT) is an intensive therapy program that has been observed to improve object and action naming after 10 treatments, after which patients may respond only with verbal output (no gestures, writing, sound effects) [17]. An opaque screen is placed on a table at which the speech-language pathologist is seated on one side and the patient on the other; there is eye contact above the screen. Each treatment lasts 3 hours. Richter et al. [18] found therapeutic success following treatment with constraint-induced aphasia therapy to be correlated with a relative decrease of activation in RH areas, including the IFG/insular cortex. After speech therapy with chronic stroke patients, new LH activation has been associated with improvement in language [19–22].

Since 1877, it has been suggested that the RH can support some language after LH stroke [23,24]. Some functional imaging studies have observed RH activation during different language tasks in a variety of aphasia patients [25–27]. In these studies, the RH activation was considered compensatory. Additionally, new RH activation has been observed following speech therapy in some aphasia patients [28–30]. Fernandez et al. [31] suggested that RH participation in the acute recovery stage of LH stroke may be followed 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. It is possible that high RH activation may be "maladaptive" and lead to a "dead-end," inefficient strategy for recovery, particularly in nonfluent aphasia patients [3,6–8,32•,33].

Whether recovery in aphasia is mediated primarily from undamaged LH language or perilesional regions or from RH language homologues (or both), the aforementioned studies suggest there is potential for brain reorganization and improved language in post-stroke aphasia [3].

Part 2. Rationale for Using rTMS in Nonfluent Aphasia

TMS

rTMS allows painless, noninvasive stimulation of the human cortex (approximately 1 cm^3 in size) from outside the skull. It uses magnetic fields to create electrical currents in cortical regions of interest (ROIs). rTMS may be used to produce changes in cortical excitability [32•]. When delivered to the same cortical region, slow (1-Hz) rTMS appears to decrease excitability in the targeted cortical ROI that lasts beyond the duration of the train itself [34], leading to measurable behavioral effects. Conversely, rapid rTMS (> 5 Hz) increases cortical excitability [35]. rTMS has been observed to affect language, ranging from facilitation of naming [36] to speech arrest [37], depending on the rTMS parameters and location of the coil.

As reviewed in Part 1, several functional imaging studies with chronic, nonfluent aphasia patients have observed high activation, possibly "overactivation," during language tasks in parts of R Broca's area and other R perisylvian language homologues, which may be maladaptive [6–8,9••,12]. When applied to a specific ROI in the undamaged hemisphere, low-frequency (1-Hz) rTMS may suppress the inhibitory process of that ROI, permitting reactivation of some areas within the damaged hemisphere and promoting some functional recovery [32•]. This is similar to the phenomenon of "paradoxic functional facilitation" (PFF) [38]. The phenomenon of PFF suggests that direct or indirect neural "damage" to a specific area in the central nervous system may result in facilitation of behavior [38]. Thus, suppressing a cortical ROI in the RH of a nonfluent aphasia patient using 1-Hz rTMS may result in a decrease in overactivation of that ROI, thus promoting less inhibition exerted by that ROI on other adjacent or distant areas, resulting in an overall modulation of the bilateral neural network for naming.

Review of our rTMS treatment protocol in nonfluent aphasia patients

Inclusion criteria

Our studies included patients with chronic aphasia who were at least 6 months post single, unilateral LH stroke. They were R-handed, were native English speakers, and ranged in age from 40 to 80 years old. They had not had a seizure for at least 1 year. Patients had nonfluent speech with a one- to four-word phrase length, as measured with elicited propositional speech on the "cookie theft" picture from the Boston Diagnostic Aphasia Examination (BDAE). Patients named at least three pictures from the first 20 pictures on the Boston Naming Test (BNT). They were requested not to receive any individualized speech therapy throughout their first year of participation in our rTMS studies.

Baseline naming testing

At entry, the baseline naming ability for Snodgrass and Vanderwart (S&V) [39] pictures was established for each patient. This baseline S&V naming score was used during phase 1 rTMS sessions (explained later) to establish the best RH cortical ROI to suppress with rTMS, to improve naming. Ten 20-item S&V lists were administered across

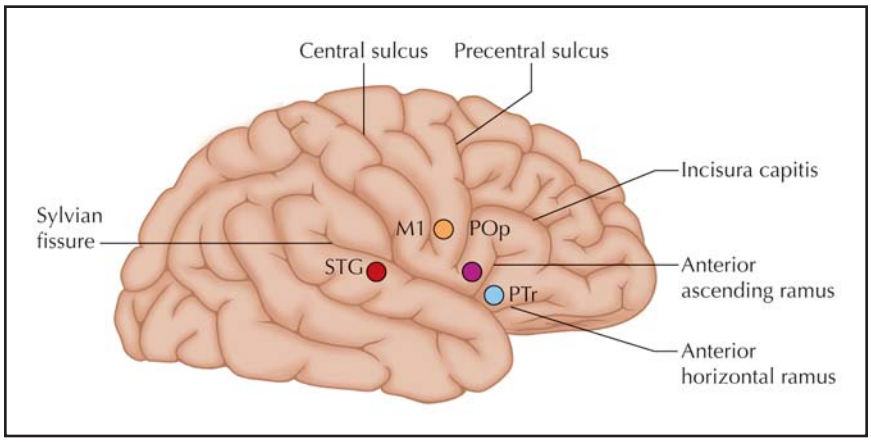

Figure 1. Right hemisphere cortical regions of interest (ROIs) examined during a phase 1 repetitive transcranial magnetic stimulation treatment protocol. The ROIs include M1, the mouth (orbicularis oris, verified with motor evoked potential), the superior temporal gyrus (STG), and subregions within Broca's area: the pars triangularis (PTr) posterior and the pars opercularis (POp). Phase 1 establishes the location of the best right hemisphere cortical ROI to suppress during phase 2 treatment.

three separate testing sessions during baseline testing. For each patient, the baseline mean and SD for response time (RT) and for number of S&V pictures named correctly across the 10 lists were calculated.

rTMS treatment (two phases)

Each patient participated in two phases of rTMS treatment. The intensity of rTMS was adjusted for each TMS session and applied at 90% of motor threshold (MT). MT is the intensity of magnetic stimulation needed to elicit a muscle twitch in the thumb, L first dorsal interosseus muscle, in 5 of 10 trials when using single-pulse TMS applied to the primary motor cortex of the contralateral hemisphere. Published guidelines for rTMS safety parameters are based on stimulation intensities expressed as a percentage of the individual's MT [40].

Phase 1 rTMS: locating the best RH cortical ROI to suppress

The location of the single, best RH cortical ROI to suppress with rTMS to improve picture naming was determined individually for each patient during phase 1, in which 1-Hz rTMS was applied at 90% MT for 10 minutes (600 pulses). A figure 8–shaped TMS coil (7-cm diameter) was used with the Super-Rapid High Frequency Magstim Magnetic Stimulator (Magstim, Carmarthenshire, Wales, UK). This rTMS protocol was applied in separate sessions to different RH cortical ROIs. ROIs examined have included the M1, mouth (orbicularis oris, verified with motor evoked potential), STG, and subregions within Broca's area: PTr posterior and POp (Fig. 1). Immediately after 10 minutes of rTMS to suppress an ROI, picture naming was assessed by administering an S&V 20-item picture list. The single RH cortical ROI associated with at least a 2-SD improvement above baseline S&V naming (obtained at entry) was considered the "best-response" RH cortical ROI for that patient.

Phase 2 rTMS: suppressing the best-response RH ROI longer, over more sessions

During phase 2, the best-response RH ROI determined for each individual during phase 1 was suppressed with 1-Hz rTMS (90% MT) for 20 minutes, 5 days per week for 2 weeks. On each day of treatment, rTMS was applied using the same Magstim device as in phase 1. A frameless stereotaxic system (Brainsight; Rogue Industries, Montreal, Canada) was used to guide the position of the TMS coil on the patient's scalp. This enabled online monitoring of the specified brain area on the patient's MRI scan throughout the rTMS session and from day to day. Coil orientation was monitored and held constant across sessions at approximately 45°. One purpose of phase 2 was to investigate the long-term effects on naming after a series of 10 rTMS treatments. Each patient received follow-up language testing at 2 months and up to 8 months after the 10th rTMS treatment. There were no negative side effects.

Results for six patients in phase 1

We observed a site-specific effect of rTMS on the number of pictures named correctly ($F = 14.63$; df 3, 5; $P = 0.0001$) and RT ($F = 5.63$; df 3, 15; $P = 0.009$), including a double dissociation within parts of Broca's area. In six aphasia patients, suppression of R PTr with 1-Hz rTMS resulted in the patients becoming more accurate, naming more pictures, and having a faster RT. However, suppression of R POp with 1-Hz rTMS resulted in patients becoming less accurate, naming fewer items, and showing an increased RT. Patients named significantly more items after 1-Hz rTMS to suppress R PTr compared with suppression of R POp (Fisher's protected least significant difference post hoc $P < 0.001$), R M1, orbicularis oris ($P < 0.01$), and R STG ($P < 0.005$) [41].

Results for four patients in phase 2

Two months after 10 rTMS treatments to suppress R PTr, four aphasia patients had significant improvement on three naming tests: 1) the BNT, first 20 items ($P = 0.003$); 2) the BDAE subtest Animals ($P = 0.02$); and 3) the BDAE subtest Tools/Implements ($P = 0.04$) [42]. At 8 months post-TMS, all three naming test scores continued to improve relative to pre-TMS testing, but only Tools/Implements was significant ($P = 0.003$). BNT and naming Animals failed to reach significance because of one patient.

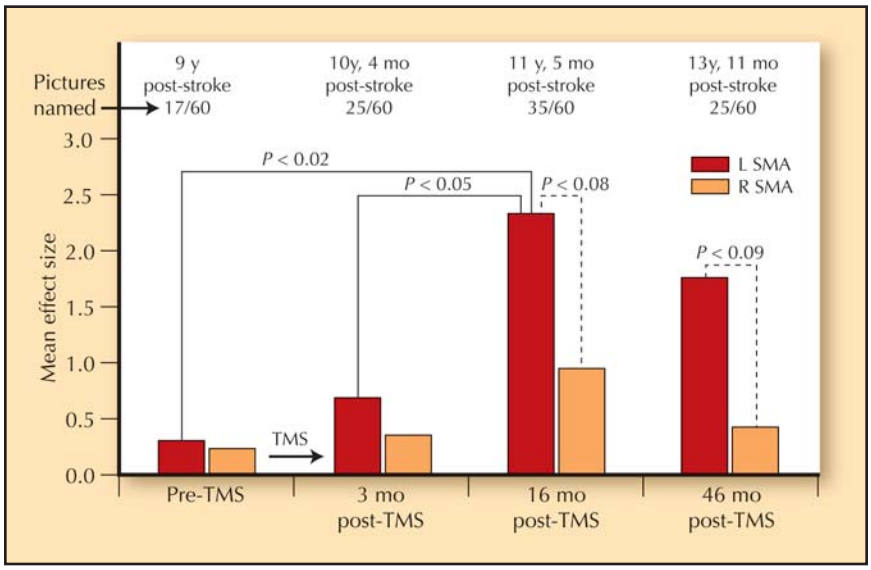

Figure 2. Overt naming functional MRI results for region of interest analysis before and after repetitive transcranial magnetic stimulation (rTMS) for patient 1, a good responder. Results are shown for scans pre-TMS and 3, 16, and 46 months post-TMS. The bar graph shows the mean effect size for left and right supplementary motor area (L SMA, R SMA) activation. There was a significant shift to greater L SMA activation at 16 months post-TMS compared with pre-TMS and at 3 months post-TMS. Greater L SMA activation remained at 46 months post-TMS.

Overt naming fMRI pre- and post-TMS in two nonfluent aphasia patients

fMRI was used to examine brain activation during overt naming before and after 10 20-minute, 1-Hz rTMS treatments to suppress part of the R PTr to improve naming in two patients with chronic nonfluent aphasia [9••]. One patient was a "good responder" with improved naming and phrase length in propositional speech, which lasted almost 4 years post-TMS. The other patient was a "poor responder" with no change in naming or propositional speech post-TMS.

Overt naming fMRI block design paradigm

Overt naming fMRI scans were obtained in the same manner as that used by Martin et al. [43]. The continuous sample, block design, overt naming fMRI paradigm took advantage of the hemodynamic response delay in which increased blood flow remains for 4 to 8 seconds after the task [44]. Task-related information is obtained after the task, minimizing motion artifact [45].

Functional imaging results for the good responder

We hypothesized that after rTMS treatment to suppress R PTr in patients with chronic nonfluent aphasia, there would be a shift in activation from RH frontal areas to new activation in LH perilesional, perisylvian areas and the L SMA if there were good response with improved naming. Patient 1 (P1), who was a good responder, showed activation in the R and L sensorimotor cortex (mouth area), R IFG, and R and L SMA before TMS as well as at 3 months and 16 months post-TMS.

At 16 months post-TMS, however, there was a significant change in SMA activation, in which P1 showed a significant increase in activation in the L SMA compared with before, and 3 months after TMS ($P < 0.02$ and $P < 0.05$, respectively). There was also a trend toward significantly greater activation in the L SMA than the R SMA at 16 months and 46 months post-TMS ($P < 0.08$ and $P < 0.09$, respectively). Before TMS, there was no difference between L and R SMA activation. It is unknown at exactly what point after TMS the shift to the stronger L SMA activation occurred for this patient during overt naming; however, the shift was first observed at 16 months post-TMS (P1's highest accuracy rate, 58% named). There were no intervening overt speech fMRI scans between 3 and 16 months post-TMS. The LH activation remained present, even at 46 months post-TMS (nearly 4 years post-TMS), when the patient was 13 years, 11 months post-stroke. On the language outcome measures, P1 improved on the BNT from 11 pictures named before TMS to scores ranging from 14 to 18 pictures after TMS (2–43 months post-TMS). His longest phrase length improved from three words pre-TMS to five to six words post-TMS (Fig. 2).

Functional imaging results for the poor responder

Before TMS (1.5 years post-stroke), patient 2 (P2) had significant activation in the R IFG (3% of pictures named). At 3 and 6 months post-TMS, there was no longer significant activation in the R IFG, but significant activation was present in the R sensorimotor cortex. Although P2 had significant activation in both the L and R SMA on all three fMRI scans (pre-TMS and at 3 and 6 months post-TMS), ROI analyses showed no difference across sessions in the L or R SMA activation.

For P2, who was a poor responder, suppression of R PTr with rTMS resulted in no new, lasting perilesional LH activation across sessions. His naming remained only at one to two pictures during all three fMRI scans. His BNT score and longest phrase length remained at one word after TMS.

Lesion site may play a role in each patient's fMRI activation pattern and response to TMS treatment. P2 had an atypical frontal lesion in the L motor and premotor cortex that extended high, near the brain vertex, with deep white matter lesion near the L SMA. This patient also had frontal lesion in the posterior middle frontal gyrus at the junction of the premotor cortex, an area important

for naming [46]. Additionally, P2 had lesion inferior and posterior to Wernicke's area, in parts of BA 21 and 37. P1 had no lesion in these three areas.

Part 3. Pilot Study: TMS Plus CILT

Results for a patient with severe nonfluent aphasia

In CILT, a program observed to improve object and action naming, patients may respond only with verbal output (no gestures, writing, or sound effects) [17]. A patient with severe nonfluent aphasia participated in our original rTMS protocol at 6.5 years post-stroke. At that time, she had improved on the BNT; her score increased from 4 before TMS to 7 and 12 pictures named at 2 and 8 months, respectively, post-TMS [33].

At 5 years, 10 months (12.5 years post-stroke) after the first rTMS series, she participated in our pilot study, in which she underwent a second series of 10 identical rTMS treatments to suppress the R PTr. However, each rTMS treatment was followed immediately by 3 hours of CILT (5 d/wk for 2 weeks) [47].

Before this intervention, her object naming was tested on a set of 250 color pictures, three times. During CILT, one third of the color pictures presented as stimulus items for therapy had never been named on pretesting (0/3), one third had sometimes been named (1–2/3), and one third had always been named (3/3).

To examine changes that might occur during intervention, BDAE naming subtests (Actions, Animals, Tools/Implements) and the BNT were administered 12 times pre-TMS; daily, immediately after each CILT session; and 10 times post-TMS. These time-series data were later analyzed using a double-bootstrap method (available at http://www.stat.wmich.edu/slab/Software/Timeseries.html). Language outcome measures used to examine long-term effects included the BDAE and BNT examined at baseline—pre-TMS (three times)—and at 1 and 6 months post-TMS. Significant improvement was defined as greater than 2 SD above baseline.

Results for the time-series analysis showed significant improvement on BDAE Action Naming ($P = 0.035$) and Tools/Implements ($P = 0.01$). On language outcome measures, there was greater than 2 SD improvement on BDAE Action Naming, Tools/Implements, and Single Word Repetition. The patient's improvement in verb action naming was observed only following the second rTMS series, which included CILT.

Part 4. DTI Study of AF Connections to Parts of Broca's Area

In our rTMS studies with aphasia patients, we have observed long-term improved naming in those with chronic nonfluent aphasia following a series of rTMS treatments to suppress the R PTr [33,42]. During phase 1 rTMS, when the R POp was suppressed for 10 minutes, we observed a temporary impairment in naming. Suppression of R POp has never been observed to be a best-response ROI to improve naming in our nonfluent aphasia patients. To better understand these results, we conducted a study with DTI involving the AF connections to these subregions within Broca's area. The AF, a pathway connecting Broca's area and posterior language zones, was studied extensively in the LH. However, AF connections to parts of Broca's area and to the vPMC have not been determined, nor have they been studied in the RH. We used DTI in eight healthy subjects (five males) to track the mid-portion of the AF to parts of Broca's area (PTr, POp) and to the vPMC (Kaplan et al., unpublished data).

We observed a significantly greater volume of fibers in the L AF than the R AF, in agreement with previous studies (for review, see Catani and Mesulam [48]). Within parts of L Broca's area, we found that eight of eight subjects had L AF connections to the POp (one subject also had L AF connections to the PTr). Within parts of R Broca's homologue, we observed R AF connections to the POp in five of eight subjects (one subject also had R AF connections to the PTr). All eight subjects had L AF connections to the vPMC, and seven had R AF connections to the vPMC. Our study showed limited AF connections to the PTr; Frey et al. [49] observed L anterior Broca's area connections to the STG to be via the extreme capsule, not the AF.

Results from our DTI study showed that in the LH, connections from the L AF are primarily to the L POp and that in the RH, connections from the R AF are primarily to the R POp. Similarly, there are multiple connections from the L AF to the L vPMC and from the R AF to the R vPMC.

Possible relevance of the mirror neuron system to aphasia recovery

The POp and vPMC are part of the mirror neuron system [50•]. Mirror neurons are cells that fire during both production and perception of similar actions. They are important in child language acquisition [51] and are bilateral, thus they may have special relevance in promoting recovery in aphasia, in which the R POp and R vPMC are always spared in cases with unilateral LH lesion.

The notion that POp is part of the mirror neuron system might help clarify why suppression of R POp in our aphasia patients (during phase 1) would impair naming, directly interrupting activation of mirror neurons, thus interfering with verbal production of names for pictures. Frey et al. [49] observed direct connections from L posterior Broca's area, via the AF, to the supramarginal gyrus. Suppression of the R POp with 1-Hz rTMS consistently produced impairment in naming, perhaps primarily because of direct suppression of the mirror neurons located there and secondarily as the indirect result of impaired connections from the POp, via the AF, to the R posterior language zones, and possibly to the LH posterior language zones.

In addition, the R vPMC also may play a similar role in aphasia recovery both primarily, as part of the mirror neuron system, and secondarily, from connections with

the AF to the posterior language zones. A recent rTMS study by Meister et al. [52] supports the role of vPMC mirror neurons as necessary for phonemic categorization in speech perception, in which there is a functional interplay between the vPMC and L STG. Although we have no rTMS data regarding the effect of R vPMC suppression on naming in aphasia patients, we posit that suppressing the R vPMC might impair naming in nonfluent aphasia patients in a manner similar to suppressing the R POp.

Conversely, we observed that suppressing the R PTr with rTMS improves naming in patients with nonfluent aphasia. Although the mechanism for this beneficial effect is unknown, we have posited the following: In cases of nonfluent aphasia in which LH lesion is present in L inferior frontal cortical and/or subcortical white matter areas, there may be hyperactivity of neurons in the R PTr as a result of interhemispheric disinhibition from the damaged L frontal lobe. Furthermore, before rTMS, the hyperactivity of the R PTr could be excessively suppressing the R POp, thus possibly hindering recovery from aphasia. Therefore, suppressing the R PTr with 1-Hz rTMS may promote less inhibition of the R POp from the R PTr via U-fibers, directly permitting better modulation of the R POp, an important part of the mirror neuron system. Better modulation of the R POp also may indirectly support better modulation of the R vPMC as well as other parts of the bilateral neural network for naming, including the RH and LH temporoparietal areas [53].

Other transcranial electrical stimulation studies

The effect of high-frequency rTMS on naming actions and objects in mild and moderate–severe Alzheimer's disease was studied recently [54]. In this investigation, 20-Hz rTMS was applied to the L or R dorsolateral prefrontal cortex areas for 500 ms while the subject was asked to name a picture on the screen. Patients with mild Alzheimer's disease showed significant improvement in naming actions only, whereas those with moderate–severe cases showed improvement in naming actions and objects.

Another electrical stimulation intervention that holds promise for patients with chronic aphasia is transcranial direct current stimulation (tDCS) [55]. Although the effect of only one session was examined, improved naming was observed, with an increase of 33.6% (SEM, 13.8%) immediately after tDCS treatment, in eight patients with chronic nonfluent aphasia. These results are similar to those from our rTMS studies in that they suggest a neural plasticity is present in chronic stroke patients with aphasia.

Conclusions

Transcranial electrical stimulation with either slow or fast rTMS or tDCS, if placed on the proper cortical target area with specific treatment parameters, can induce changes in language behavior, particularly naming. Our rTMS results in patients with chronic nonfluent aphasia support the notion behind PFF [37]; that is, a new, temporary "virtual" lesion (as with 1-Hz rTMS) can improve behavior in chronic stroke.

With the exception of our rTMS studies with nonfluent aphasia patients, studies with transcranial electrical stimulation have applied only a single session of treatment. It is suggested that more treatment sessions be applied over longer periods. Functional imaging studies before and after TMS contribute information toward the understanding of the plasticity of neural networks for language and recovery. The overt speech fMRI data with our nonfluent patient with good response to TMS support the hypothesis that restoration of parts of the LH language network is linked, at least in part, to better recovery of naming and phrase length in nonfluent aphasia. Additional fMRI studies before and after TMS are warranted. Also, combining electrical stimulation (rTMS or tDCS) with speech therapy sessions provided immediately afterward might promote further language improvement in a variety of patients with chronic aphasia.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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