

Post-Stroke Aphasia and RTMS Treatment (PART)

Study Protocol & Statistical Analysis Plan

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**POST-STROKE APHASIA AND RTMS TREATMENT (PART) STUDY
NIH R01 HD068488**

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PART Study Protocol

This study will test two hypotheses:

Hypothesis 1: Navigated excitatory rTMS (nerTMS) will improve language outcomes when applied to the peri-stroke language areas identified by fMRI in patients with chronic (>1 year) aphasia caused by a left middle cerebral artery (LMCA) stroke when compared to sham treatment (ST); synergistic effect is expected in subjects treated with a combination of nerTMS and CIAT. Treatment response, as measured with qualitative and quantitative aphasia testing (AT), will depend on treatment duration.

Hypothesis 2: Improved language performance will be associated with increased left-lateralization of language networks following nerTMS as assessed by fMRI. This left-hemispheric shift of language processing will correlate with behavioral response to nerTMS, representing evidence of clinical efficacy; the degree of the post-intervention recovery will correlate with the degree of the left-sided language shift.

The following specific aims were designed to test these hypotheses:

Aim 1 (treatment): To determine the comparative efficacy and optimal dosing of nerTMS on aphasia recovery using a randomized, double-blind, sham-controlled study design. Subjects (15/group) will be randomly assigned to 4 treatment groups: (a) 3 weeks of nerTMS, (b) 1 week of ST+ 2 weeks of nerTMS, (c) 2 weeks of ST+1 week of nerTMS, or (d) 3 weeks of ST (control group). This design will allow systematic evaluation of the efficacy of nerTMS and its most optimal dose for language recovery. Short- and long-term outcomes will be evaluated with aphasia testing (AT) and fMRI.

Aim 2 (imaging): To use fMRI to assess changes in language lateralization in response to nerTMS. We will examine the relationship between the degree of pre-nerTMS language lateralization (fMRI) with the post-nerTMS language outcomes (AT) and determine whether fMRI language lateralization can predict AT performance following nerTMS targeted to the left middle cerebral artery (LMCA) stroke areas.

Aim 3 (exploratory/shaping): To explore the possible synergistic effect of constraint induced aphasia therapy (CIAT) plus nerTMS on aphasia recovery in a group of 20 LMCA stroke patients. These subjects will receive 2 weeks of nerTMS enhanced by 1 hour of daily CIAT; both therapies will be administered in open-label fashion. Patients will be evaluated with fMRI and AT as above and compared to the arm "b" of the double-blind study and to CIAT data collected in an ongoing study (R01 NS048281). This aim will gather preliminary data regarding the possible synergistic effects of nerTMS and behavioral intervention.

SIGNIFICANCE

Stroke patients tend to prioritize speaking, writing and walking as the three most important rehabilitation goals. Of note is that two of these goals involve communication. This underscores the significance of developing a successful approach to aphasia treatment for the several hundred thousand new aphasia patients each year and over 1 million stroke survivors with aphasia in the U.S. alone.

Post-stroke aphasia and its impact

Aphasia, defined as an impaired ability to communicate, is one of the most feared symptoms of stroke. It is associated with high mortality, significant motor impairment, and severe limitations in social participation [22-26]. During the past three decades science has made great strides in developing acute treatment strategies that, in some patients, decrease or eliminate stroke-related deficits. Unfortunately, the progress in aphasia rehabilitation research has not kept pace with the development of acute therapies. Current therapy approaches are based largely on developing alternative compensatory strategies for lost functions rather than restoring them [27]. Of the ~700,000 ischemic strokes occurring annually in the United States, about 1/3 are estimated to present with aphasia as one of the symptoms; for these patients, the chances of recovery after the initial period are relatively poor [28, 29]. When substantial recovery does occur, it tends to be within the first 2 to 10 weeks. Function recovery 12 months after stroke, is thought to be very unlikely [15, 30]. Of the ~270,000 people with post-stroke aphasia only 1/3 recover sufficiently to reenter society as productive members; the majority of them develop long-term aphasia with the persistent deficits that interfere with continued productivity. Many are not able to communicate or perform activities of daily living because of this handicap and become dependent upon their families and society. These stroke victims and their families are in dire need of additional restorative therapies that will enable the stroke patients to return to society as productive members. Our preliminary data suggest that nerTMS may become one of those therapies, a finding we hope to further develop in this dosing study, which is the next logical step in advancing this field.

Repetitive transcranial magnetic stimulation (rTMS)

In general, rTMS involves repeated brain stimulation at regular frequencies; it is a noninvasive method of exciting or inhibiting neurons through repeated induction of weak electric currents in the brain via rapidly changing magnetic fields. If used with appropriate intensity, brain activity can be modulated using rTMS without discomfort or ill effects [31, 32]. The cortical plasticity induced by rTMS is thought to be primarily related to two mechanisms that are dependent on the location and frequency of the regular-rate rTMS stimulation: 1) ipsilesional excitatory stimulation of the affected hemisphere exerts its effect via decreases in the GABA-ergic inhibition, and 2) inhibitory rTMS applied to the unaffected hemisphere downregulates local GABA activity to remove the inhibition of the affected hemisphere by the unaffected hemisphere exerted via transcallosal connections; both mechanisms are further modulated via increased activity of the excitatory NMDA system (direct long-term potentiation) [33-36]. The stimulation area is usually very focal [37] and the changes induced by rTMS can persist well beyond the duration of the stimulation [16, 36].

Excitatory rTMS (erTMS) applied to the dominant hemisphere

Excitatory rTMS (usually >5Hz) has been shown to facilitate language processing via increased short- and long-term cortical excitability; nerTMS applied to the left-hemispheric speech area facilitated naming in healthy controls [17, 20], Alzheimer's disease [18], and Primary Progressive Aphasia [19]. In general, as a treatment, rTMS has been shown in numerous pilot studies to be efficacious in various neurological (e.g., migraine [44]) and psychiatric (e.g., depression) conditions [45-49] and is now FDA-approved for the treatment of depression. This suggests that the use of nerTMS to increase the use of dominant-hemisphere language circuits may indeed underlie improved language skill (AIMS 1 and 3).

Individualized Navigation and Theta-Burst Stimulation (TBS)

This study's proposed use of both a neuronavigational system and TBS pulses represents a significant practical and scientific advance. Neuronavigation enables targeting to each patient's area of maximum residual function as determined by fMRI. This technology also enables reliable, three-dimensionally precise reapplication of TMS throughout the study. TBS is a lower intensity modification of traditional rTMS. Therefore, TBS is more comfortable for the patient [50] and, consequently, easier to blind to a sham. The TBS TMS pulse sequence mimics electrical firing in the hippocampus underlying long term potentiation (LTP). This TMS method has comparable excitatory effects to 5 Hz rTMS but may have some theoretical advantages in a longer term treatment study. A single session of excitatory TBS over the affected hemisphere has been shown to transiently improve motor function after chronic stroke [51, 52]. Our preliminary data obtained at the University of Cincinnati using the same nerTMS protocol as proposed in this study indicate that a navigated, daily, 2-week trial of nerTMS may improve language function in chronic aphasia. Thus, a study evaluating the efficacy of 1, 2, or 3 weeks of TBS is most likely to provide an answer regarding the optimal treatment duration.

Safety of rTMS protocols in healthy and stroke subjects

Early reports [53, 54] of possible seizures associated with TMS led over 10 years ago to the development of safety rules regarding stimulation frequency, intensity, train duration and intertrain interval [55, 56]. Multiple subsequent studies of rTMS have demonstrated this to be a safe technique for use in studies of stroke [57-60] and even in epilepsy [61-64]. In healthy adult studies, TBS has been well tolerated with no seizures or epileptiform EEG activity induction; only one study reported a seizure in a healthy subject caused by TBS stimulation with intensity set at approximately 120% of a motor threshold, a threshold far exceeding the proposed here settings [65]. Our preliminary data also demonstrate the safety of the nerTMS protocol; no adverse reactions were observed in our pilot group of stroke patients despite 10 daily 10-minute long nerTMS (TBS) sessions. Therefore we are confident in proposing nerTMS as a safe and potentially highly beneficial intervention in patients with chronic aphasia after stroke.

Functional MRI for language localization in post-stroke aphasia

If increased activation of dominant-hemisphere language circuits, stimulated by nerTMS, underlies a greater degree of improvement in language function then fMRI may be able to identify and observe these underlying changes in neural circuitry. Post-stroke neuroimaging studies that have evaluated recovery from aphasia in adults with unilateral lesions show evidence of cortical reorganization and migration of language functions to the non-dominant hemisphere after a dominant hemisphere insult [12, 13, 66]. Interestingly, one study that showed such a redistribution pattern using PET and fMRI language tasks also found negative association between increased non-dominant inferior frontal gyrus activation and recovery after an ischemic stroke [67]. The best recovery was observed in patients with peri-infarct activation on the fMRI and PET studies.

Winhuisen et al. (2007) applied inhibitory rTMS to the non-dominant language circuits and found that post-stroke aphasia recovery was dependent on the preserved left-hemispheric language centers rather than on recruitment of the non-dominant homologues [68]. Two recent studies showed that the fMRI activation may be dependent on the phase of post-stroke recovery with early right-hemispheric upregulation of the fMRI signal changes correlating with language recovery and late consolidation of the

activation in the left-hemispheric language centers [69, 70]. These and other studies support the presence of preexisting language pathways in both, the dominant and non-dominant hemispheres and suggest that in healthy conditions the circuitry in the non-dominant hemisphere is inhibited by the active circuitry in the dominant hemisphere; when the preferred pathway is interrupted (as in a stroke), the non-dominant circuitry is uninhibited, hence activated. These studies, including studies from our group, suggest that increased reliance on language circuits in the dominant hemisphere supports higher levels of recovery from aphasia after stroke [12, 13]. Navigated excitatory rTMS applied to the identified by fMRI language areas is expected to facilitate and augment the increased reliance on these areas for post-stroke aphasia recovery; language mapping with fMRI pre- and post-rTMS can be used to document its effect and to predict the likelihood of post-intervention recovery (AIM 2).

Post-stroke aphasia rehabilitation methods

Post-stroke recovery may be facilitated by appropriate restorative interventions. Traditional therapies encourage the use of multi-modality compensatory strategies with an expectation that the use of these strategies will decrease as language capabilities increase. Several such strategies have been developed such as Conversational Prompting, Promoting Aphasics Communicative Effectiveness (PACE), and use of communication boards, drawing, or computer therapy. These non-linguistic systems do improve immediate overall communication ability, but there is no evidence that compensatory strategies truly aid the recovery of language functions; in fact, they may simply contribute to learned non-use. Paradoxically therefore, current rehabilitation strategies may irrevocably reinforce the deficits found in post-stroke aphasia. More advanced strategies for aphasia rehabilitation that directly address language skill improvements rather than compensatory strategies are being developed (e.g., CIAT; R01 NS048281; PI: Szaflarski). CIAT was recently introduced as a potential new method for post-stroke aphasia rehabilitation [71, 72]. It is modeled on a physical rehabilitation program for recovery of motor deficits called constraint-induced motor therapy (CIMT) [73, 74]. The overall philosophy of this type of therapy is to prevent function disuse by forcing patients to utilize the affected function while avoiding compensatory non-use strategies [75]. Even in patients with chronic stroke, these therapies have led to clinical improvements associated with cortical plasticity [7, 76] confirming that there is no firm age limit to cortical plasticity. Specifically, CIAT is defined as a systematic constraint of verbal and nonverbal communication modalities coupled with massed practice of targeted language skills [77, 78]. In the CIAT protocol, communicative behaviors are gradually guided toward more complex linguistic communication. The constraints are imposed by the structure of the introduced material, which includes the "rules formulated by the therapist and by shaping and modeling" (Pulvermüller et al., 2001, p. 1623) [77] with significant increases in language skills noted when compared to conventional therapy. Our preliminary data suggest that the CIAT protocol recently implemented in the ongoing R01 (Szaflarski, PI) may be successful in improving language function in aphasic patients [79]. There is also some suggestion that different treatment approaches may work synergistically; subgroup analysis of an otherwise negative study suggested possible beneficial effects of erTMS combined with CIMT [59]. Due to the low number of participants, significant variability in the enrolled subjects (sub-cortical vs. cortical strokes) and lack of fMRI guidance for erTMS in that study, there is a strong indication for evaluating nerTMS combined with CIAT compared with either intervention alone (AIM 3). [59]. Finally, a recent study used CIAT to shape post-stroke aphasia therapy with Memantine [80]. While Memantine was an efficacious treatment, Memantine + CIAT group had the best outcome supporting that the approach proposed in this study of combining 2 treatment strategies may be of an incremental benefit.

INNOVATION

The challenge for this study is to further develop and implement nerTMS as a tool for stimulating language recovery in patients with chronic post-stroke aphasia. This challenge will be addressed by conducting a randomized, sham-controlled, dose-response trial of nerTMS in order to provide class I data from a phase III treatment trial investigating fMRI-targeted treatment for chronic post-stroke aphasia (**AIM 1**). While there is evidence that nerTMS applied to the affected hemisphere may improve post-stroke motor recovery [58] and when applied to the language-dominant hemisphere in controls may promote better language skills, nerTMS has not been tested in treatment of post-stroke aphasia or in combination with other restorative therapies (CIAT; **AIM 3**). The potential impact of this study is tremendous with the potential to improve the quality of life in hundreds of thousands of Americans. We will demonstrate that nerTMS applied to the peri-stroke regions defined by fMRI promotes language recovery, and we will determine the most efficacious and the safest dose of nerTMS (**AIM 1**). Further, while the fMRI methods developed and tested by us and others are now well established, the approach of using fMRI to localize targets for nerTMS intervention and as a way of predicting the possibility of post-stroke recovery ("point of no return"; **AIM 2**) is innovative; accomplishing this aim will establish fMRI as a clinical tool in rehabilitative medicine and allow its use for identifying intervention targets.

Figure 1 below illustrates the randomized, double-blind, sham controlled dosing trial of rTMS for the treatment of aphasia (**AIM 1**).

Figure 1. Diagram of the proposed nerTMS double-blind treatment protocol (**AIMS 1-2**) and associated testing ("AT" qualitative and quantitative AT; AT – quantitative testing only).

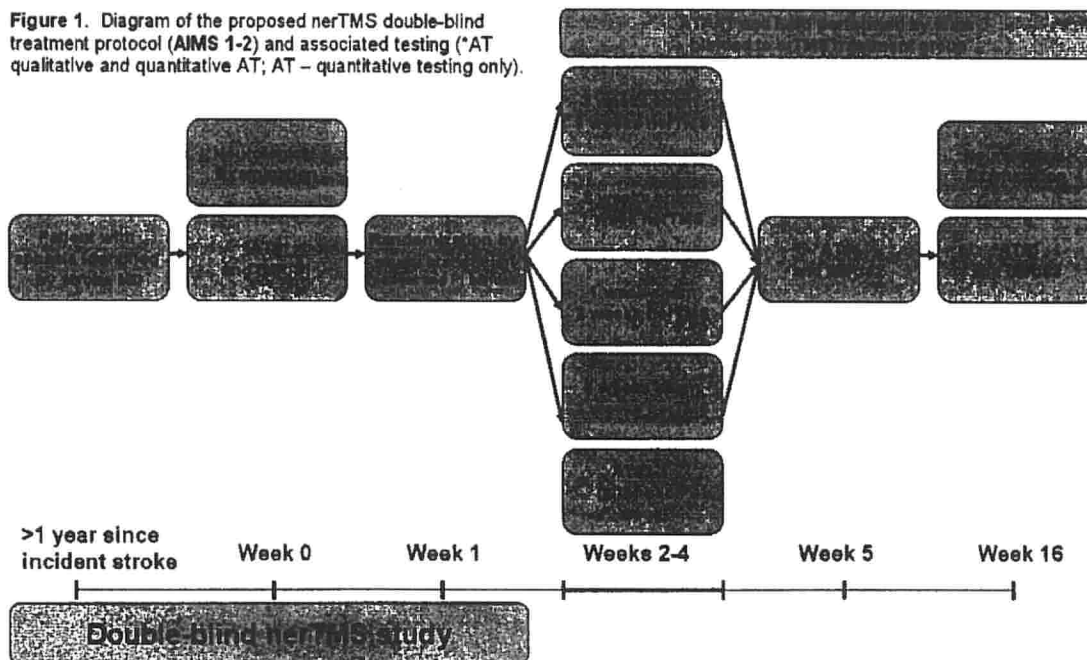


Figure 2 below illustrates the open-label study of combined rTMS and CIAT for the treatment of aphasia (AIM 3).

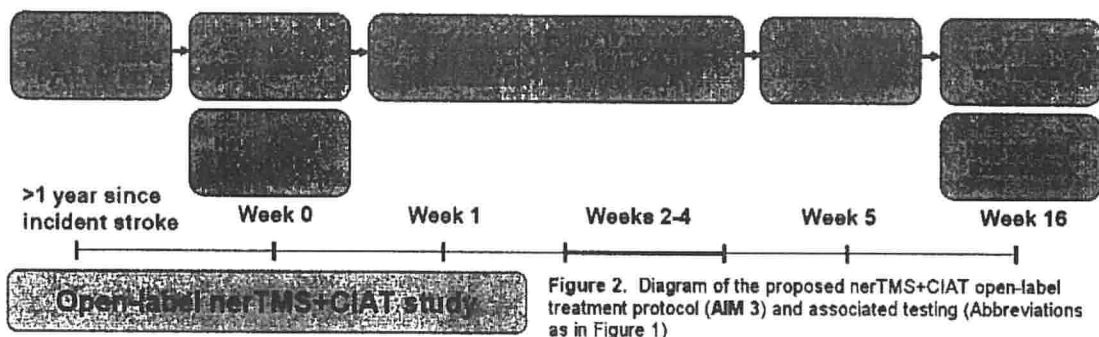


Figure 2. Diagram of the proposed nerTMS+CIAT open-label treatment protocol (AIM 3) and associated testing (Abbreviations as in Figure 1)

DETAILED STUDY PROTOCOL

DAY 1 (enrollment)

Subject identified by study personnel (or referred to our team for possible study participation by clinicians in the area) will undergo screening for study participation:

The inclusion criteria are:

- Age \geq 19 years
- LMCA stroke as indicated by the presence of aphasia and MRI lesion in the LMCA distribution
- Moderate aphasia (Token Test score between 40th and 90th percentile)
- Fluency in English
- Provision of written informed consent by the patient and/or the next of kin

The exclusion criteria include:

- Age less than 19 years
- Underlying degenerative or metabolic disorder or supervening medical illness
- Severe depression or other psychiatric disorder
- Positive pregnancy test in women of childbearing age
- Any contraindication to MRI/fMRI at 3T (i.e., intracranial metal implants, claustrophobia)
- Any contraindication to nerTMS (e.g., seizures or epilepsy)

Screening will also include a complete medical history, details of the precipitating event, physical examinations, complete baseline and ongoing vital sign assessments, neurological evaluations, laboratory results and diagnostic imaging performed. Screening assessments will be performed by the clinician involved in the care of the patient to determine subject eligibility criteria especially neurological examination, which will be documented as part of the patients' medical record.

For the randomized controlled trial (RTC; Figure 1), once informed consent and HIPAA authorization for research are obtained, the subject will be randomized. Randomization will be conducted by the study biostatistician and will be implemented using a standard sealed envelope process.

For the un-blinded observational study (OBS; Figure 2), once informed consent and HIPAA authorization for research are obtained, the subject will be scheduled for group therapy with CIAT where rTMS will be used as a primer for improved rehabilitation outcomes. Three to four subjects will be scheduled concurrently in order to achieve the required minimum of 3 subjects per CIAT therapy group. These subjects will not be randomized or blinded to the treatment.

A member of the research study staff will monitor the subjects for continued compliance with Inclusion and Exclusion Criteria. Those subjects who do not meet the continuation criteria will be terminated from the study.

DAY 2 (pre-nerTMS; days 1 and 2 may be combined)
All subjects (RTC or OBS) will undergo the same procedure

Data Collected for Study Enrollment (after signed consent):

Upon Admission:

Demographics

Medical history (including any chronic underlying disease and medications)

Contact information to include phone number

Time, date, and mechanism of stroke

Neurological Examination (see below)

Neuropsychological testing of aphasia will include:

| Procedures | NAT 1 | NAT 2 | NAT 3 | NAT 4 | NA T 5 |
|---|----------|----------|----------|----------|-----------|
| Test Version | A | B | A | B | A |
| Boston Naming Test | X | X | X | X | X |
| Semantic Fluency Test (letter & category) | X | X | X | X | X |
| Controlled Oral Word Association Test (COWAT) | X | X | X | X | X |
| BDAE Complex Ideation subtest | X | X | X | X | X |
| Peabody Picture Vocabulary Test III (PPVT III) | X | X | X | X | X |
| Cognitive-Linguistic Quick Test (CLQT) part of neuro exam | X | | | | X |
| Token Test | X | | | X | X |
| WAB-R (AQ) (picture description-verbal discourse sample— see below) | X | | | X | X |
| Apraxia Subtest | X | | | X | X |
| BDAE Picture Description (written discourse sample) — see below) | X | | | X | X |

Verbal Discourse Prompt (WAB-R)

Take a few minutes to look at this picture. When you are done, I want you to tell me a story about what you see happening. (Set timer to 2 minutes).

If participant states he/she is ready before two minutes provide the following cue: *You have a little more time to look at the picture to help you tell a story. Use this time to help develop your story.*

When the two minutes is up, say, *"Tell me your story."*

Written Discourse Prompt (BDAE)

Take a few minutes to look at this picture. *When you are done, I want you to write me a story about what you see happening. (Set timer to 2minutes).*

If participant states he/she is ready before two minutes provide the following cue: *You have a little more time to look at the picture to help you write a story. Use this time to help develop your story.*

When the two minutes is up, say, *"Write your story."*

Discourse samples will be elicited by the tester prior to, immediately after, and 3 months after intervention (nerTMS). These tests will be administered as part of the aphasia testing. Testing procedures will be audio and/or video recorded.

DAY 3 (may be combined with previous procedures)
All subjects (RTC or OBS) will undergo the same procedure

Functional MRI

fMRI Scanning Procedures have been refined over the course of our experiences with numerous healthy and stroke subjects undergoing studies of language [3, 4, 12-14, 85-93]. These procedures provide high success rate in the completion of fMRI experiments. All subjects will undergo standard radiology screening for MRI compatibility at 3T. The subjects will be carefully oriented to the equipment and will engage in explicit practice of all of the tasks' requirements. We will utilize the following fMRI language paradigms:

Language task #1 (block design verb generation task; BD-VGT)

Language task #2 (event-related verb generation task; ER-VGT)

Language task #3 (semantic/tone decision task; SDTD)

Additional language tasks may be obtained dependent on the results of the neuropsychological aphasia testing.

Language task #4 (paired associates verbal learning task; ER-VLT)

Language task #5 (sentence/picture matching task; ER-ASL)

The total duration of the fMRI procedure will be less than 1 hour which is usually very well tolerated by stroke subjects. Upon completion of the fMRI procedure fMRI data will be processed and forwarded to the rTMS laboratory for entry into the stereotactic system for guidance of the rTMS intervention.

NEXT 3 WEEKS INCLUDE EITHER THE SHAM CONTROLLED BLINDED RTMS STUDY (RTC)

OR

NEXT 2 WEEKS INCLUDE THE COMBINED RTMS AND CIAT INTERVENTION (OBS)

DESCRIPTION OF THE PROCEDURES FOR BOTH IS PROVIDED BELOW

RTMS PORTION

Depending on study assignment (**RTC** or **OBS**) subjects will receive nerTMS as per protocol (Figures 1 and 2):

To test the effect of nerTMS on post-stroke language recovery, we will apply an excitatory stimulation protocol termed "theta burst stimulation" (TBS) to the language areas detected by fMRI in the hemisphere affected by stroke.

RTC: We will apply up to 15 TBS treatments made up of 15 sham, 5 TBS + 10 sham, 10 TBS + 5 sham, or 15 TBS treatments, depending on study arm.

OBS: We will apply 10 daily TBS treatments per participant. Four OBS subjects will receive rTMS and CIAT (see below) within approximately one hour of each other, with the treatment sequence permuted so that, on average, the time between nerTMS and CIAT for each subject will be the same.

Using theBrainsight (TM) Neuronavigation System, coil placement will be targeted individually to the left frontal lobe area (Broca's area) as identified by fMRI. The following previously developed protocol will be followed:

1. Single-pulse TMS is performed to establish resting motor threshold (RMT) and active motor threshold (AMT) with a Magstim 200R stimulator connected through a BistimR module to a 70 mm figure-8 coil.
 - a. RMT is defined as the minimum stimulus intensity that produces a motor evoked response (about 50 μ V in 50% of 10 trials) at rest.
 - b. AMT is defined as the minimum stimulus intensity that produced a motor evoked response (about 200 μ V in 50% of trials) during isometric contraction of the tested muscle at about 10% of maximum force.
2. Surface electromyography (EMG) leads are placed over the first dorsal interosseous (FDI) muscle of the left hand. The coil is placed over the primary motor cortex in the right hemisphere at the optimal site for obtaining a MEP in the FDI.
3. After the RMT and AMT are determined, iTBS is performed using Magstim Rapid2R with intensity set at 80% of AMT obtained from the right hemisphere.
4. The figure-8 coil is positioned tangentially to the skull, with the handle parallel to the sagittal axis pointing occipitally.
5. iTBS consist of bursts of three pulses at 50 Hz given every 200 milliseconds in two second trains, repeated every 10 seconds over 200 seconds for a total of 600 pulses.
6. BrainSight™2 is used for neuronavigation to guide rTMS stimulation to the fMRI-identified residual left hemispheric Broca's area.

The coil will be positioned tangentially to the skull, with the handle parallel to the sagittal axis and pointing occipitally. Since the level of stimulation used in this protocol is subthreshold, blinding will be maintained independent of the study arm. This portion of the study will be supervised by the rTMS team.

CIAT PORTION (OBS group only – AIM 3)

CIAT portion of this aim will be conducted at our original CIAT site in the speech laboratory at the Taub Treatment Clinic by trained Speech Language Pathologists using the previously developed and validated protocol [7].

All treatment materials were developed and validated previously [7] and are currently in use in our laboratory (R01 NS048281; PI: Szaflarski). Wooden card holders will be used to provide a horizontal layout of cards and a partial barrier from other participants, but will not obstruct participants' view of the clinicians or the other participants. We have previously determined that all participants and clinicians need to see each other for two reasons: (a) The participant needs to control his constraint of non-verbal behaviors without an unnatural device, and (b) the communication activity needs to resemble natural social interaction [7]. This is because the theory behind CIAT indicates that part of the reinforcement for increasing verbal output is the receipt of positive social feedback as a result of successful communication.

The enrolled chronic stroke subjects will receive the previously implemented CIAT protocol (R01 NS048281; PI: Szaflarski) [7]. Since this protocol is standard we only briefly describe it here. During each session, 2 speech therapists will be involved in the CIAT treatment group. Given the results of the pretreatment evaluation the clinicians will collaboratively set individual language goals. Each participant's program will be designed to:

- (a) determine linguistic strengths,
- (b) identify what cues are beneficial,
- (c) select behavior(s) to constrain, and
- (d) promote a linguistic target.

Speech Language Pathologists will review the pretreatment quantitative and qualitative aphasia testing (AT) results in order to identify what language skills exist (i.e. strengths). Then, the clinicians will make note of the type of aphasia and of what types of cues elicit more accurate responses. Individual non-verbal communicative behaviors will be identified as the behaviors to constrain. Meanwhile, the clinicians will select one or two linguistic targets as language goals. During the treatment session, clinician will determine whether any of these targets need to be modified. Daily CIAT session lasting 45-60 minutes will be conducted for 10 days (2 weeks) within 1 hour (on average) of completion of nerTMS. Prior to each session, the participants will be instructed on their linguistic target(s) specific to her/his own aphasia type. The clinician will provide appropriate cues. We found from our preliminary study that tracking of participant responses to cueing within the session was a critical element in determining treatment and modification of goals and constraints [7]. Each participant will take turns requesting a card from a player of his choice. The responding player will then pass the card while producing a verbal statement appropriate to his language level. If the responding player does not have the card, then the turn ends. To provide incentives, we will award a point for each round, with prizes at the end of each day to the player with the most points. These incentives are intended to increase the participants' interest in the treatment. This portion of the study will be supervised by Ms. Marbury and Ms. Johnson.

POST-INTERVENTION PROCEDURES

1. Neuropsychological aphasia testing
2. Functional MRI procedures
3. Neurological exam

All procedures will be performed within 1 week of the last rTMS/CIAT intervention and then 3 months later following the above described protocols.

Upon completion of the above procedures subjects will be dismissed from the study. Further follow up will be provided by primary neurologist or primary care provider.

NEUROLOGICAL EXAMINATION

Standard neurological examination will be performed by Dr. Mark or his designee at the initiation of the study (after the patient signs the consent form) and after completion of the study (around the time of final neuropsychological testing of aphasia ~3 months after completion of the intervention). This examination will include:

| | Study enrollment | Study termination | Change* |
|---|------------------|-------------------|---------|
| Date of exam | | | |
| Vital Signs | | | |
| Blood Pressure | | | |
| Heart Rate | | | |
| Finger stick blood glucose | | | |
| Cranial nerve examination | | | |
| Visual fields | | | |
| Ophtalmoscopic examination | | | |
| Pupils | | | |
| Eye movements (CN 3,4,6) | | | |
| Facial symmetry | | | |
| Auditory assessment | | | |
| Palate | | | |
| Shrug | | | |
| Tongue examination (midline) | | | |
| Muscle strength right upper extremity (MRC) | | | |
| Muscle strength left upper extremity (MRC) | | | |
| Muscle strength right lower extremity (MRC) | | | |
| Muscle strength left lower extremity (MRC) | | | |
| Muscle stretch reflexes right upper extremity | | | |
| Muscle stretch reflexes left upper extremity | | | |
| Muscle stretch reflexes right lower extremity | | | |
| Muscle stretch reflexes left lower extremity | | | |
| Coordination right upper extremity | | | |
| Coordination left upper extremity | | | |
| Gait | | | |
| | | | |
| Mechanism of ischemic stroke** | | | |
| | | | |

* (-1 = worse after intervention; 1 = improved after intervention; 0 = no change)

** (small vessel = 1; large vessel = 2; embolic = 3 ; hypercoagulable state = 4; unknown = 5)

Participants requiring additional protections

Regarding cognitively impaired subjects: All subjects will be enrolled in the study based on voluntary basis. The patients will not be approached until the purposed of the study is explained to the patient by the physician directly involved in the care of the patient and a verbal permission is obtained from the patient (and family member/significant other if appropriate) regarding the contact with the study personnel. After screen is complete and the subject is found to be eligible, she/he will receive the consent form for review. After at least 24 hours the patient will be contacted regarding the study. If interested and have correctly answered all questions on both the Consent Form

Comprehension Questionnaire and the Subject's Statement of Consent and Authorization form, consent will be obtained from the patient and/or family member/significant other.

Patients may also self-volunteer (self-refer) for the study. In such a case, their physicians may not be involved in the referral process but all other procedures as listed above will be observed.

Subject Travel and Recruitment

A compensation of \$75.00 per fMRI scan/testing will be offered to each family for their participation in the study. This will be in the form of cash reimbursement for travel to and from the Center for Imaging Research and parking fees and will be paid at the end of each fMRI visit. We believe this compensation will be necessary in order to help families to justify the visits to the imaging center (3 visits per stroke patient; approximately 3-4 hours of their time per visit is required to participate in the study; \$225.00/patient).

Subjects will also be reimbursed for participation in the nerTMS or nerTMS+CIAT studies. Since these visits are much shorter and require on average 1-2 hours per visit, a \$25.00 stipend per visit per patient is allotted for this purpose (15 visits per double-blind study patient = \$375.00/patient and 10 visits per open-label study patient = \$250.00/patient). This will be paid in cash at the end of each treatment week.

DATA SAFETY MONITORING PLAN

The data and safety monitoring plan for the proposed study will include monitoring of efficacy data by an independent Data Safety Monitoring Board (DSMB) and monitoring of tolerability data, including adverse events and serious adverse events, by the study investigators as well as the independent DSMB and the University of Cincinnati IRB.

The DSMB will include:

1. Statistician (Jun Ying, PhD)
2. Physiatrist with extensive experience in post-stroke rehabilitation (Kari Dunning, PhD)
3. Stroke neurologist (Pooja Khatri, MD)
4. Neurologist with extensive experience in neuropsychological testing (Michael D. Privitera, MD).

All these individuals already expressed their interest in participating in the Data Safety Monitoring Board for this study. Drs. Lindsell and Szaflarski will be responsible for providing updated efficacy and tolerability data to the DSMB every six months (at least 2 weeks prior to the DSMB meeting). The DSMB will assess the risks and benefits of study participation to all subjects and based on this assessment the DSMB will provide a written report of their analyses and recommendation as to whether the study should continue, whether modification to the study are needed or if the study should be terminated. Dr. Szaflarski, in conjunction with the DSMB, will be responsible for making certain that the DSMB files their report to the IRBs and NINDS. The DSMB will also provide the investigator with a summary of their report that will include their recommendations.

Adverse events will be monitored during the study using clinical interviews and examinations that will be administered by a board certified neurologist (Dr. Mark) who has had more than 10 years experience conducting clinical investigations of stroke in adults. Dr. Mark (or in his absence another experienced neurologist) will be responsible for evaluating all adverse events during study visits, which will occur at the beginning and the completion of the study or more frequently as necessary. Further, the rTMS Team will supervise all nerTMS sessions and report any adverse events to the PI. Additionally, a study related physician (typically, Dr. Szaflarski) is accessible by pager to patients, their legal guardians, hospital and research staff 24 hours/day, 7 days/week. Drs. Szaflarski will be responsible for monitoring all baseline and post-baseline assessments.

An adverse event (AE) is any unexpected medical occurrence in a patient or clinical investigation subject who is administered a treatment (nerTMS and/or CIAT) and which does not necessarily have a causal relationship with the treatment. This includes any clinical change that occurs at any time following consent that does not typically occur in that subject and is considered clinically significant. The frequency and severity of all observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded throughout the study. Dr. Szaflarski, with oversight from the DSMB, will be responsible for determining causal relationship between the study treatment and all AEs.

Withdrawal from the study as a result of an AE or because of therapeutic measures taken to treat an AE will be at the discretion of Dr. Szaflarski. If a subject withdraws or is withdrawn from the study for any reason, Dr. Szaflarski will monitor subjects with any

ongoing AE until the AE is resolved or determined to be stable. All AEs (including those present during screening) will be reported. However, for analytics purposes, only post-baseline (randomization) AEs will be considered for calculating treatment group differences in AEs.

A serious adverse event (SAE) is any adverse experience occurring at during study participation that results in any of the following outcomes: death; a life threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences when, based on appropriate medical judgment of the study physician, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgment of whether a particular AE meets the above criteria for an SAE for the proposed study will be determined by Dr. Szaflarski, in conjunction with the proposed DSMB. It will also be Dr. Szaflarski's responsibility to manage all SAEs and to make referrals for appropriate care, as necessary. All SAEs will be reported to the University of Alabama at Birmingham Institutional Review Board, the study DSMB, and the NINDS project officer within 72 hours of their discovery. The study blind may be broken at any point throughout the study as needed to protect the safety of a subject. All subject information will be de-identified when reporting SAEs. All AEs and SAEs will be entered into a database that is de-identified and password protected to ensure confidentiality. Dr. Szaflarski, in collaboration with Dr. Mark, will ensure that all patients have appropriate follow-up care after their study participation.

Subjects participating in the proposed study will receive standard treatment that meets (or exceeds) the quality of treatment available in the community. Repetitive TMS (rTMS) is currently approved for the treatment of depression; although it is not approved for the management of post-stroke aphasia, many studies support its use in this clinical setting. However, patients/legal guardians will be told that rTMS is not currently FDA approved for this indication or population in which it is being used. The proposed study does not require an IND submission, since it meets the following requirements of the Center for Drug Evaluation and Research: (1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug; (2) it is not intended to support a significant change in the advertising for the product; (3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; (4) it is conducted in compliance with the requirements for UAB IRB review and informed consent; (5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs/treatments; and (6) it does not invoke 21 CFR 50.24 (exception from informed consent requirements for emergency research).

Finally, the trial will be registered at www.clinicaltrials.gov.

DSMB – manual of operation

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2. Primary Responsibilities of the DSMB
3. Membership of the DSMB
 - a. Members
 - b. Conflicts of Interest

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 - d. Minutes of the DSMB Meeting
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1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for protocol "Post-stroke aphasia and rTMS treatment (PART) study".

The Charter will define the primary responsibilities of the DSMB, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of the Open and Closed Reports that will be provided to the DSMB.

2. Primary Responsibilities of the DSMB

The DSMB will be responsible for safeguarding the interests of trial participants, and assessing the safety and efficacy of the interventions during the trial (rTMS and or combined rTMS and CIAT). This responsibility will be exercised by providing recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMB will be advisory to the principal sponsor-investigator Jerzy P. Szaflarski, MD, PhD. The PI will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. *If an investigator does not agree with the DSMB recommendations then a memo justifying the reasons for not complying with the recommendations must accompany the minutes.*

3. Membership

- a. Members

The DSMB will consist of at least 4 independent clinicians and biostatisticians that, collectively, have experience in the management of patients with strokes associated with aphasia and in the conduct and monitoring of randomized clinical trials. A quorum will require at least 3 members, including the chair.

DSMB Chair: Kari Dunning, PhD
CAHS Rehabilitation Sciences
Kari.dunning@uc.edu
513 558 7483

Biostatistician: Jun Ying, PhD
Department of Public Health
Jun.ying@uc.edu
513 558 2767

Other DSMB Members:

Pooja Khatri, MD
Department of Neurology
Pooja.khatri@uc.edu
513 558 6411

Michael D. Privitera, MD
Department of Neurology
Michael.privitera@uc.edu
513 558 5440

Conflicts of Interest

The DSMB membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, study investigators are not members of the DSMB.

The DSMB members will disclose conflicts of interest to fellow members. Any DSMB member who has or develops a significant conflict of interest should resign from the DSMB.

DSMB membership is for the duration of the clinical trial. If any members leave the DSMB during the course of the trial, the PI will promptly appoint their replacement.

4. Timing and Purpose of the DSMB Meetings

The first meeting of the DSMB will occur 3 months after study initiation (official date of the IRB approval). The reviews will be done in person or via teleconference. The study team is responsible for coordinating the venue for the DSMB meetings, i.e. establishing the meeting date and time, reserving the conference room, arranging for teleconference equipment. The purpose of the DSMB meetings is to review the conduct of the trial to date and assess safety and efficacy of the study intervention (rTMS). The DSMB will review SAEs and determine whether the study should be prematurely discontinued.

Ad hoc meetings may be scheduled as needed.

5. Confidentiality

A format for Open and Closed Sessions should be implemented. The intent of this format is to enable the DSMB to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMB and study team. DSMB personnel will not have access to unblinded data; group comparisons will be provided by study statistician (Dr. Lindsell).

The study arm assignment for individual participants may be disclosed on a case-by-case basis. Request to unblind must be provided by DSMB Chair in writing. The DSMB will have responsibility for assessing and making recommendations to correct any possible abuses of the disclosure privilege.

6. Communication

Open Session

The Open Session provides the DSMB an opportunity to query the study team about issues that have arisen during the review of the data.

Closed Session

Sessions involving only DSMB membership and the independent biostatistician who generated the Closed Reports will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. The DSMB will develop a consensus on its list of recommendations, including whether the trial should continue.

DSMB Meeting Minutes

Depending on the issues and protocol, a DSMB meeting may have both Open and Closed meeting minutes. Meeting minutes should be distributed as soon as possible after the DSMB meeting. IRB needs to be included on the distribution list. At the time of IRB annual renewal, DSMB minutes will be required, if not already provided.

7. Statistical Monitoring Guidelines

Study will not be terminated if there is evidence that one of the treatment conditions has better side effects profile or efficacy unless statistically significant difference in favor of one of the treatment arms is observed in at least 50% of the variables.

8. Content of Reports for the DSMB

- Study number and title. Brief summary of the study design.
- Protocol amendments
- Status of accrual. If accrual is slower than expected, a plan for increasing enrollment.
- Status of participating sites (for Multi-Center trials)
- Compliance