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Effects of rTMS on Brain Activation in Aphasia

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A. Background and Significance:

Aphasia is a neurogenic language disorder that is present in approximately one third of acute stroke patients [1], with 60% of cases persisting into the chronic phase (> 6 months post stroke) [2]. Aphasia not only impacts interpersonal communication, but also participation in activities of daily living, independence and autonomy [3]. Furthermore, aphasia severity is positively associated with higher rates of depression and lower health related quality of life (HRQoL), a measure of an individual's perceived physical and mental well-being [4-5]. Lower HRQoL is associated with increased rates of disease-specific morbidity and mortality independent of traditional risk factors [6-9] and critically, *improvements* in HRQoL have been associated with decreased risk [9]. Therefore, decreasing the communicative impairment associated with aphasia has the potential to have broad and significant consequences on Veteran's health.

Encouragingly, a growing number of studies are finding that aphasia therapy is effective well into the chronic phase although treatment response between individuals remains highly variable [10]. It is crucial to understand why some people with chronic aphasia benefit from treatment more than others in order to refine intervention approaches and improve outcomes. One factor that is hypothesized to contribute significantly to the degree of individual language recovery is cortical reorganization, although the most beneficial patterns of reorganization, or how to best induce them, are still under debate. This study proposes to investigate the ability of repetitive transcranial magnetic stimulation (rTMS) to elicit functional cortical reorganization associated with improved language function in study participants with chronic aphasia. The results from this study will both extend existing knowledge regarding the brain-basis of language recovery and inform how rTMS can best be applied to encourage reorganization-related recovery in chronic aphasia.

A1. Effect of hemispheric recruitment on language recovery in aphasia

For the majority of individuals, language is supported by a strongly left- lateralized network of brain regions. When a left hemisphere (LH) stroke injures any of the brain regions involved in this network, other regions are recruited in a compensatory fashion via functional cortical reorganization. There is considerable evidence that compensatory recruitment of undamaged left hemisphere perilesional brain regions results in more optimal recovery of language functions than does recruitment of regions in the right hemisphere (RH) [11-14, and many others]. Furthermore, recruitment of LH perilesional regions, specifically left frontal regions, predicts treatment-related increases in correct naming for individuals with chronic aphasia [15-16].

One account for the poorer outcomes related to RH contralesional recruitment has been framed in terms of interhemispheric inhibition. In its undamaged homeostatic state, the LH language network actively inhibits the RH during language-related tasks via transcallosal projections [17]. This is thought to be an adaptation due to LH specialization, and hence optimization, for language tasks, particularly language production. According to this account, when the LH network is damaged as a result of a stroke, the RH is released from this inhibition, allowing it to be recruited during language production tasks. The now overactive RH in return inhibits the preserved perilesional cortical areas in the LH, preventing them from being recruited [18-19]. As the RH is less specialized for language, this hemispheric shift in activation may result in improved language abilities during recovery, albeit improvements that are relatively suboptimal compared to those that result from more efficacious LH perilesional recruitment [13].

A2. Application of non-invasive brain stimulation to optimize cortical reorganization

Based on the inhibition hypothesis described above, several relatively recent studies have used an approach called repetitive transcranial magnetic stimulation (rTMS) to encourage LH perilesional recruitment for language in people with aphasia following stroke. rTMS is a non-invasive brain stimulation technique in which a focal, time-varying magnetic field is applied to a specific brain area to induce neuronal depolarization. rTMS can be used to selectively target a given brain region with a resolution as focal as 0.5 cm^3 [20]. Typically, administering a slow (1 Hz) sequence of magnetic pulses via rTMS temporarily reduces cortical excitability in the targeted brain region [21]. Researchers have therefore used 1 Hz rTMS to inhibit the right hemisphere overactivation postulated by the inhibition hypothesis and thus allow for LH perilesional recruitment [12-24, and others; see 25 for meta-analysis, 19 for review].

The area that is most frequently selected as the target of inhibitory rTMS is Pars Triangularis (PTr) in the inferior right frontal lobe. RH PTr has been characterized as an especially disruptive node in the RH compensatory network that in addition to inhibiting the LH, exhibits less efficient and dysfunctional processing compared to its LH counterpart [26-27]. Consistent with this view, a recent meta-analysis of functional neuroimaging studies in aphasia found that RH PTr was the only right frontal brain area that was not activated under the same conditions as its LH counterpart [28]. Support for this approach has been reported by Naser and colleagues [29] who found that naming abilities immediately improved following one session of inhibitory rTMS to RH PTr, but not when applied to other perisylvian RH areas. Although the improvements resulting

from a single session of inhibitory rTMS are transient, studies in which RH PTr has been targeted across repeated sessions have affected naming improvements that accrue over time and persist after the termination of rTMS administration [30-31]. These longer-lasting changes in the dynamics of the language network are possibly a consequence of mechanism changes in the effectiveness of synapses between cortical neurons, similar to long term depression/potentiation [32]. Thus, language use even outside of the direct context of the rTMS session serves to reinforce the more functional LH-focused language network and consequently, to discourage recruitment of the maladaptive RH one [28]. This view is further supported by the observation that improvements in language measures continue significantly *beyond* the conclusion of rTMS administration, up to several years [33].

A3. Potential sources of response variability to rTMS

A.3.1 Baseline cortical excitability

Despite the strong positive evidence for the effectiveness of inhibitory rTMS to RH PTr to improve naming in chronic aphasia, not every individual responds significantly [34]. One potential explanation for this finding is that the effect of 1Hz rTMS is state dependent. That is, it has a stronger inhibitory effect when administered to a brain region that has a higher level of excitability [35]. For example, the inhibitory effect of 1 Hz rTMS is *stronger* and *lasts longer* when participants move their hand prior to rTMS stimulation of the portion of the motor cortex containing the representation of the hand. Perhaps more importantly, inhibitory rTMS has been found to have a paradoxical *excitatory* effect when applied to brain regions already in a state of inhibition [36].

Researchers in the stroke motor-recovery literature have controlled for the potential paradoxical effect of 1 Hz rTMS by first administering a 6 Hz rTMS pulse sequence. In contrast to slow rTMS, pulse sequences above 5 Hz have an excitatory effect [37]. This excitatory pulse sequence in essence “primes” the targeted brain region so that the 1Hz pulse sequence has the expected inhibitory effect, while at the same time enhancing the effect [38]. To date, only one study has applied an excitatory priming sequence to control for potential varying levels of cortical excitability in aphasia. In this study by Kakuda and colleagues [39], participants received 10 minutes of 6 Hz priming stimulation prior to 20 minutes of 1 Hz low-frequency rTMS to RH PTr every weekday for two consecutive weeks. The rTMS was followed by 60 minutes of speech-language therapy (SLT). Improvement was noted for all four participants on both receptive and expressive language measures following the series of rTMS sessions. However, this study had several critical limitations, most notably that all participants received speech-language therapy as part of the protocol. It is therefore impossible to determine the source of the measured improvements (the rTMS, the SLT, or their interaction). In addition, as all participants received the excitatory priming sequence, the study was unable to conclude whether the excitatory priming produced any additional benefit above and beyond that of the standard 1Hz rTMS protocol.

It is highly likely that pre-rTMS RH PTr excitability *would* differ between individuals with chronic aphasia depending on the extent to which it is recruited during recovery. If an individual with chronic aphasia retained some function of LH PTr, which would be expected for those individuals without left frontal lesions, they would not be expected to demonstrate a large amount of compensatory recruitment of RH PTr [28], and hence show little benefit from rTMS induced inhibition of this area. In fact, Kakuda and colleagues in a different study [40] found that the location of peak activation during functional magnetic resonance imaging (fMRI) of a repetition task was in the left hemisphere perilesional areas for over half of the participants with chronic aphasia in their study. *Therefore, it is imperative to have pre-rTMS neuroimaging measures of levels of RH PTr activation in order to accurately interpret the rTMS effects.*

A.3.2 Extent of left-hemisphere focused shift in activation

There is little direct neuroimaging evidence to support the hypothesis that inhibitory rTMS to RH PTr promotes recruitment of intact LH perilesional cortical areas. Several of the rTMS studies in aphasia that measured functional activation did so only *prior* to rTMS and did not investigate pre-post rTMS changes [40-41]. To date there have been only two studies that have investigated differences in task-related regional brain activation *before* and *after* inhibitory rTMS to RH PTr in order to test this hypothesis. Martin and colleagues [34] found that, for one participant, a LH shift in activation post-rTMS corresponded to improved naming, whereas for the other participant, for whom no naming improvement was seen, no such activation shift was noted. Despite offering support for the inhibition hypothesis, this study has several significant limitations. First, the authors used a blocked functional magnetic resonance imaging (fMRI) design to measure naming-related brain activation. Although the block design offers more power to detect small effects, neural responses to individual trials within a block cannot be evaluated separately. This is especially important when evaluating lateralization of activation during naming as other studies have noted differences in lateralization for correct compared to incorrect naming responses in chronic aphasia [26]. Secondly, post-rTMS fMRI scans were only performed beginning at 3 months after rTMS conclusion. Because of this delay, it is unclear whether the

observed activation changes are a cumulative result of the multiple rTMS sessions (via the LTD-like effect), experience-dependent reinforcement of the newly recruited areas within the LH language network, or both. Finally, the study included only 2 participants, limiting the statistical power and analyses that could be performed as well as the generalizability of the findings to a broader group of individuals with chronic aphasia.

A case study published by Turkeltaub and colleagues [27] evaluated the immediate neurobiological effects of inhibitory rTMS. The single participant performed an overt naming task (identical to the one used by Martin et al [30] discussed above) while undergoing an fMRI scan immediately prior to and following the first rTMS session in a series. The rTMS immediately reduced activity at the site of stimulation (RH PTr), but no corresponding LH laterality shift was observed. Furthermore, a subsequent RH stroke further worsened the participant's aphasia symptoms, suggesting that some RH areas exclusive of RH PTr were involved in the initial rTMS induced recovery. However, this evidence is indirect and does not preclude both RH and LH recruitment, nor does it suggest that RH recruitment is *as efficient* as LH recruitment.

Finally, no studies to date have directly tested the claims of the inhibition hypothesis regarding the effect of rTMS on directional inhibitory influences between the RH and LH. To evaluate these claims it is important to measure not only activity changes but also *interactivity* changes to see how the *system* is changing as a result of rTMS across time. Furthermore, as no study has yet collected functional neuroimaging measures throughout the rTMS time course, it is impossible to infer how the acute effects of rTMS relate to the cumulative effects of multiple rTMS sessions, or longer-term changes that occur weeks and months after the conclusion of rTMS.

In summary, inhibitory rTMS targeting RH PTr appears to be a promising approach to treating language difficulties, particularly naming deficits, in chronic aphasia. However, before regular clinical use of rTMS can be considered, we need to have a better understanding of both the *potential sources of response variability*, and the *neurobiological mechanisms* underlying the beneficial effects of rTMS.

B. Preliminary Studies

Preliminary data was collected from a pilot subject (M, 44yo, 15 yrs post-onset) following the procedures described below, with the following exceptions: (1) functional activation results were limited to overall naming responses > crosshair fixation, because correct naming responses could not be uniquely distinguished (the Optoacoustics sound-cancelling microphone that will be used for this purpose (see details in "Other Support") has since been received, installed, and tested); (2) two-month follow-up data have not yet been acquired. The participant tolerated all 10 sessions of the rTMS well and experienced no adverse events.

From pre-rTMS to post-rTMS testing, the participant demonstrated significant naming improvements ($p < 0.05$) on the Philadelphia Naming Test (PNT). Table 1 presents raw scores and scores estimated using an item response theory model and scaled to mean = 0, sd = 1 [42]. As predicted, these behavioral improvements corresponded to a decrease in activation in the targeted brain region (RH PTr) from baseline (Figure 1; significant occipital activation clusters reflect increased visual processing for picture vs crosshair presentation) to post-TMS (Figure 2). This change in RH PTr activation was maintained at post-treatment (Figure 3). Notably, the post-treatment activation map (Fig. 3) obtained seven days after the final rTMS session is remarkably similar to the activation map obtained immediately following the first session of rTMS (Fig. 2), suggesting that the acute effects were consolidated, resulting in longer-term network-level change. Contrary to predictions, the naming improvements did not correspond to increased LH activation, but rather RH temporal activation. Of note is the significant size of this participant's LH lesion, involving a large portion of the LH frontal, parietal, and temporal lobes. This LH lesion may simply have been too extensive to allow for LH

Time Point	Items Named Correctly (of 175)	IRT Score Estimate
Baseline	87	-0.467 (0.13)
Post-Treatment	104	-0.096 (.0.13)
Difference	+17	+0.371 (0.19)

Table 1: Performance on the Philadelphia Naming Test

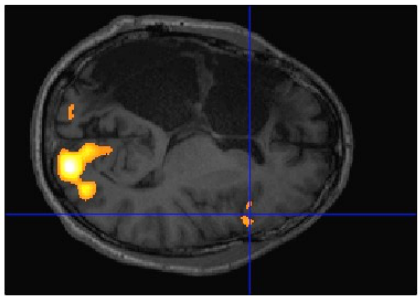


Figure 1: Baseline naming>crosshair

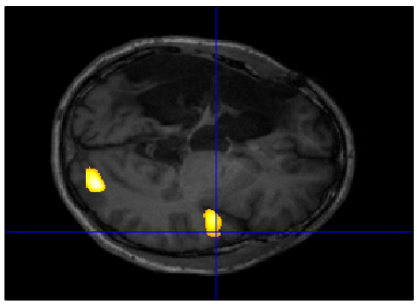


Figure 2: Post-TMS naming>crosshair

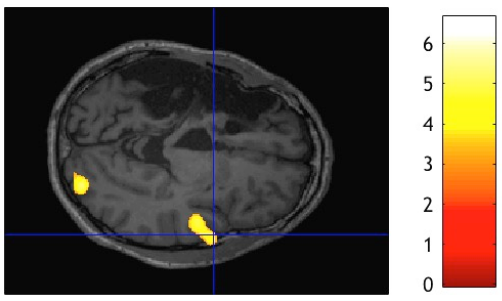


Figure 3: Post-Treatment naming>crosshair

recruitment, instead resulting in RH-supported recovery, perhaps upon release from *intra*-hemispheric inhibition by the maladaptive RH PTr. This conclusion is further supported by the TMS-induced *rightward* shift in laterality index for this participant (-0.37 at baseline, -0.6 at post-rTMS, and -0.69 at post-treatment), likely reflecting *increased* RH temporal activation in the context of relatively stable LH activation. These findings critically establish the feasibility and potential efficacy of the proposed intervention, but they leave open the question of whether TMS would have been *more* beneficial for participants with more intact LH cortex.

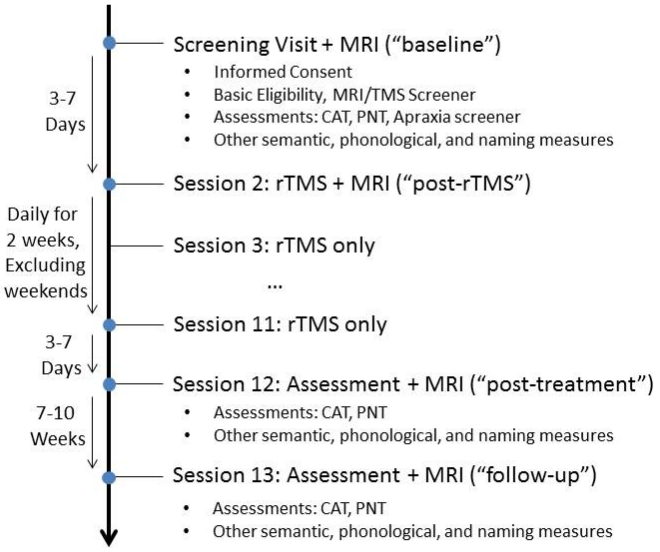
C. Research Design and Methods

In order to address the limitations of existing research as outlined above, the proposed study will employ a longitudinal, randomized parallel group design with the following goals: 1) Investigate the effect of slow 1Hz rTMS to RH PTr on naming in the *absence of adjuvant speech-language therapy,* in order to isolate the effects of the rTMS, 2) Apply a 6-Hz excitatory rTMS pulse sequence to RH PTr prior to the inhibitory 1Hz sequence for *half* of the participants. This will allow for a direct comparison of the strength of the inhibitory effect of the 1Hz rTMS between conditions (priming vs. no priming), as well as control for any unanticipated paradoxical excitatory effects, 3) Take a *longitudinal approach,* by acquiring measures of functional brain activation during naming at several time points during the rTMS series: prior to rTMS (obtain baseline levels of RH PTr activation), immediately following the first session (to evaluate acute effects), after the completion of the rTMS series (to evaluate cumulative effects), and two months post-rTMS (to evaluate long-term changes), 4) *Significantly increase the sample size,* in order to be able to perform within- and across-group statistical analyses that compare the reliability and efficacy of LH compared to RH recruitment and changes in directed interhemispheric inhibition (effective connectivity).

Several methodological considerations will allow for a more accurate account of the patterns of functional activation for the participants with aphasia. First, an event-related study design will be used in which brain responses to correctly and incorrectly named items can be distinguished and compared across time-points [26]. Secondly, measurements of hemodynamic response (HRF), which are used to estimate the neural response related to the naming event, will be calculated for each individual participant. This is important because individuals with aphasia are known to have delayed HRF or HRF that is decreased in amplitude, resulting in erroneous or underestimated measures of brain activity when canonical HRF estimates are used [43]. Third, dynamic (activity-dependent), directional coupling, known as effective connectivity, will be estimated for regions in the RH and LH to measure interactivity changes across time resulting from rTMS.

C.1 Procedures:

The schedule of study procedures across the 13 study sessions is summarized in Figure 4. During the initial session, enrolled participants will be assessed with the Philadelphia Naming Test (PNT; [44]) and the Comprehensive Aphasia Test (CAT; [45]). In cases where apraxia of speech is suspected, the Apraxia Battery for Adults (ABA-2; [46]) may be administered in whole or in part. Participants may also be assessed with other psycholinguistic and naming measures. The first session will conclude with the baseline MRI scan (described in detail below). If, following the screening session, a participant is found to be eligible they will be scheduled for all remaining study-related visits.



The second visit will begin with the first rTMS session (also described below) which will then be followed directly by the post-rTMS MRI scan. Starting the following day, the subsequent nine sessions will consist only of rTMS for a total of 10 rTMS sessions. The sessions in the rTMS series will take place daily across two weeks excluding weekends. A post-testing session, scheduled the week after the final rTMS session, will include an MRI scan and repeat administration of the language assessments that were administered during the screening visit. A final follow-up session, identical in design to the post-testing session, will be scheduled in an additional 7-10 weeks. All study-related evaluations will be administered by the PI (a licensed speech-language pathologist) or in Year 2 by the staff speech-language pathologist. Study participants will receive up to $275 for time and local travel expenses and up to an additional $1500 to defray lodging expenses incurred as part of study participation, to be pro-rated if they do not complete all study procedures (including follow-up visits).

Participants will be pseudo-randomly assigned to an rTMS treatment group (priming stimulation vs no priming stimulation) depending on the outcome of their baseline fMRI (described in C1.1, below). That is, an equal number of participants with and without baseline RH PTr activation will be approximated in each group.

C.1.1 MRI Procedure

fMRI Overt Confrontation Picture Naming Task. Images will be acquired using a 3.0 Tesla parallel-acquisition, echo-planar equipped Siemens MRI scanner. Participants will lay supine in the scanner wearing hearing protection and over-ear headphones. Their heads will be secured with foam padding to minimize movement.

During the fMRI session, picture stimuli will be projected onto a screen placed at the rear of the MRI scanner with E-Prime 2.0 (Psychology Software Tools) software, which subjects will be able to see via a head coil-mounted mirror. Participants will be asked to name the pictures aloud as quickly and accurately as possible. Picture stimuli will consist of black and white line drawings of objects drawn from the Center for Research in Language International Picture Naming Project Database (CRL-IPNP; [47]) and will exclude any items that overlap with the CAT and PNT to avoid repetition effects. The pictures will be presented for 2000 msec with a between-picture ISI between 4-16 seconds, jittered by 2 second intervals. Including longer ISIs will allow the HRF to intermittently return to levels approaching baseline in order to more accurately model individual HRF responses. Between pictures, participants will be asked to fixate on a black crosshair that will be centered on the screen. Naming responses will be recorded via a MR-compatible fiber-optic dual-channel noise cancelling microphone (Optoacoustics Ltd.) to allow for offline scoring of both accuracy and response latency. The fMRI scan will consist of 4 runs (experiment segments) of approximately 40 pictures each; with each run lasting approximately 5 minutes. Picture stimuli will be balanced across runs for average item difficulty [42]. The design of this task is similar to the design used by Postman-Caucheteux and colleagues [26] with participants with aphasia, suggesting that it is feasible with this population.

C 1.2 TMS Procedure

We will use a Magstim Rapid or Rapid2 Magnetic Stimulator (Woburn, MA) with the MagStim Double 70 mm alpha coil, to generate the pulses used to find the motor threshold, and the Magstim Double 70mm air cooled coil to generate the pulses of the rTMS treatment during this study. Before starting each treatment, subjects will be instructed to insert earplugs to lessen any possible adverse effect on hearing.

Motor Threshold and Intensity Determination. To standardize TMS stimulation intensity prior to rTMS, a resting motor evoked threshold (MT) will be established based on a distal upper extremity motor response. The MT will be measured by delivering single stimulations to the motor cortex with gradually increasing intensity no more frequently than every 3 sec, i.e. ~0.3 Hertz. Threshold is defined as the lowest intensity of stimulation producing motor evoked potentials of at least 50μV (or a visible movement of the digit) in 5 of 10 trials. Our standard stimulation intensity will be 90% of the MT.

Individual fMRI-based coil targeting. Evidence suggests that the degree of spatial resolution required to target specific cortical sites such as the PTr is achieved more readily when rTMS is used in conjunction with image-guided navigation techniques [48]. This stereotactic targeting also ensures more consistent coil placement across sessions. Following individual determination of stimulation intensity, coil placement individually targeted to the RH PTr will be performed using a frameless stereotactic method as described in Neggers and colleagues [49] and will be implemented in the BrainVoyagerQX software neuro-navigation package. Following coil positioning, participants will receive rTMS treatment according to their group assignment (see below).

TMS Administration.

Group A: Inhibitory only rTMS group: Inhibitory 1Hz rTMS will be applied continuously for 1200 pulses (20 minutes) 5 days per week across 2 weeks (10 sessions total).

Group B: Excitatory primed rTMS group: The inhibitory sequence described above will be preceded for each session by priming stimulation which will consist of intermittent 6-Hz rTMS applied in 5 second trains with 25 second intervals between trains for a total 600 pulses (10 minutes).

C2. Data Analysis

C2.1 Analysis of Behavioral Measures: Naming data (item-level performance on the PNT) will be used for analysis of rTMS treatment effects by group. Accuracy data will be analyzed using multilevel linear or logistic regression in R. Models will include fixed effects of session (baseline, post-treatment, follow-up), and group (Group A, Group B) and random effects of subject and item. Analyses may include additional random-effects structure if needed to improve model fit.

C2.2 fMRI Processing/Data Analysis: All processing will be performed using SPM12 (The Wellcome Trust Centre for NeuroImaging, UCL, UK). The concatenated functional image sequences (runs) will be preprocessed with standard fMRI analysis routines that include slice time acquisition correction, realignment,

registration to structural images, spatial normalization, and spatial smoothing. The data will also be filtered for low frequency scanner drift.

Within-subject data (first level) will be analyzed using a general linear model with a finite impulse response (FIR) basis function to model the individual HRF. For each participant, we will generate an individualized map of brain activity for the contrast of naming > baseline (crosshair fixation) including factor of MRI session for both correct and incorrect responses. Movement parameters will be entered as regressors of no interest to control for participant head movement in the scanner. Activation maps for all contrasts will be thresholded to p=0.05 (cluster corrected using Family-Wise Error (FWE)). Resulting contrast values (effect sizes) for each contrast will be entered into a second level/random effect analysis by group (Group A: inhibitory only rTMS vs Group B: excitatory primed inhibitory rTMS). Region of Interest (ROI) analysis will be performed to estimate activation for RH PTr for all described contrasts using the MarsBaR toolbox for SPM.

To assess the relative contribution of the right versus left hemisphere (hemispheric lateralization) to the fMRI naming task, whole brain laterality indices (LI) will be calculated for each scan using the LI-toolbox for SPM [50]. As LI calculation relies on the computation LI= (Left-Right) / (Left+Right), a negative value indicates a right hemispheric dominance and a positive value indicates a left hemispheric dominance. LI values will be generated using t-maps from the first level analyses described above.

Dynamic causal modeling (DCM) will be used to estimate effective connectivity changes due to inhibitory rTMS across time. Regions to be included in the DCM analysis will be derived from clusters of contiguous voxels surviving an omnibus F-test for the effect of interest (correct naming > crosshair fixation) at $p<0.001$ uncorrected from the first-level fMRI analysis. Regions will be constrained to only include those clusters that fall within the traditionally outlined “language network” in the LH (inferior frontal lobe, temporal lobe, and portions of the inferior and posterior parietal lobe, [51]) and the corresponding RH homologues. The effective connectivity model (estimate of coupling and weights between these regions) will be estimated via post-hoc network discovery methods [52]. This method uses Bayesian model selection methods to select the model that was the most likely to have generated the time series data from all possible combinations of bi-directional connections between the regions. Coupling weights for interhemispheric connections will be summed for each participant for each scanning session. Other post-hoc analyses of the DCM results may be undertaken to explore both inter- and intra-hemispheric network level effects of the rTMS.

Finally, change in naming accuracy on the PNT across sessions will be correlated with change in LI, functional activation in RH PTr, and interhemispheric effective connectivity across sessions. A positive correlation between naming gains and 1) a left-hemisphere directed LI shift, and 2) a decrease in RH inhibition of LH (more positive RH to LH directional coupling weights) will support Hypothesis 1a and 1b, respectively. A positive correlation between the magnitude of pre-TMS RH PTr activation and 1) decrease in RH PTr activation across scan sessions, and 2) magnitude of left-hemisphere directed LI shift will support Hypothesis 2a and 2b, respectively. A significant interaction of group and session (analysis C2.1) suggesting that Group B receiving the 6 Hz primed inhibitory rTMS showed greater naming improvement across time will support Hypothesis 3.

Study timeline: Average estimated participant enrollment length is 10-14 weeks including follow-up, therefore participant recruitment will conclude 4 months prior to last planned data collection. Planned enrollment will be 6 participants in Year 1 and 10 in Year 2. The accelerated enrollment will be made possible in Year 2 due to the proposed hiring of an additional 5/8 staff speech-language pathologist who will assist with participant recruitment, assessment, analyses, and manuscript preparation. Further, as ASPRR has a current enrollment of 133 individuals with aphasia (84 Veterans), and the VAPHS clinical service has historically received approximately 8 new outpatient aphasia treatment referrals per quarter, this enrollment target is feasible.

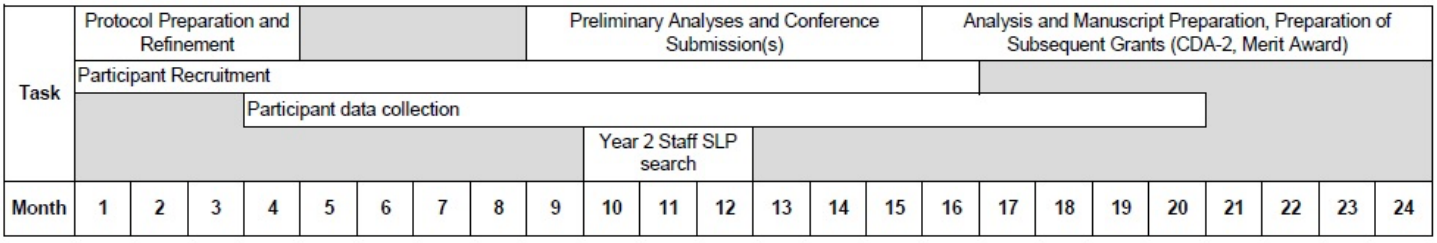


Table 2: Study timeline

Future Directions: If the proposed study is successful, a subsequent Merit Review application will investigate: 1) use of rTMS to augment treatment gains for well-established behavioral interventions; 2) connection of regions modulated by rTMS to prominent neurocognitive models of naming; and 3) relationships between changes in functional (effective) and structural (white matter) brain connectivity. Addressing these goals will both inform theoretical understanding of aphasia recovery and bring rTMS closer to direct clinical applicability.