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Continuous theta burst stimulation over right pars triangularis facilitates naming abilities in chronic post-stroke aphasia by enhancing phonological access

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) has been used experimentally to facilitate naming abilities in individuals with chronic post-stroke aphasia. However, little is known about how rTMS confers clinical improvement, hampering its therapeutic value. The present study investigated the characteristics of naming failure that improve following administration of continuous theta burst stimulation (cTBS)—an inhibitory form of rTMS—to the right pars triangularis (rPTr) in persons with chronic aphasia.

Methods: Eleven participants with chronic aphasia following left hemisphere stroke named pictures prior to and immediately following cTBS of the rPTr and a control site (vertex) in separate sessions. Prior to stimulation, we obtained two baseline measurements of picture naming ability to determine the extent and type (i.e., phonological vs. semantic) of naming impairment. Items presented for naming during stimulation were those that were named incorrectly in one or both of the baseline sessions (i.e., inconsistent vs. wrong items, respectively). Analyses assessed whether cTBS effects differed depending on the severity and/or type of naming impairment.

Results: Relative to vertex, cTBS of the rPTr improved naming of inconsistent, but not wrong, items for individuals with more severe baseline naming impairment. Critically, baseline phonological but not semantic naming impairment severity marginally correlated with improved accuracy overall, and significantly correlated with decreased phonological errors following rPTr stimulation.

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Disclosure

The authors report no potential conflicts of interest.

Conclusion: CTBS of the rPTr enhances naming by facilitating phonological access during word retrieval, indicating that individuals whose naming impairment is localized to this stage of processing may be most likely to benefit from this rTMS approach.

Keywords

continuous theta burst stimulation; neurorehabilitation; aphasia; naming impairment

1. Introduction

Aphasia, the acquired inability to produce and/or comprehend language, is a common cognitive impairment following left hemisphere stroke, affecting more than one million individuals in the United States alone. Aphasia has a profound impact on the affected individuals and their families, often resulting in decreased independence in daily activities and overall perceptions of quality of life (Tennant, Geddes, Fear, Hillman, & Chamberlain, 1997; Cruice, Worrall, Hickson, & Murison, 2003). Currently, speech-language therapy (SLT) is the most commonly employed treatment for aphasia. Although intensive SLT can improve some aspects of language and functional communication (Brady, Kelly, Godwin, Enderby, & Campbell, 2016), its effects on long-term outcomes are only modestly beneficial, leaving many aphasic individuals with life-long communication difficulties. The emergence of noninvasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS), as focal interventions that can potentially facilitate recovery from chronic post-stroke aphasia provides a promising avenue for language rehabilitation (for reviews, see Chrysikou & Hamilton, 2011; Coslett, 2016; Hamilton, Chrysikou, & Coslett, 2011; Shah, Szaflarski, Allendorfer, & Hamilton, 2013; Torres, Drebing, & Hamilton, 2013; Turkeltaub, 2015). However, little is known about which specific aspects of language difficulties NIBS techniques target (cf. Medina et al., 2012), rendering it difficult to advance more tailored approaches that involve specific and efficacious treatment protocols. Here, we explored the characteristics of language impairment that improve following rTMS to better understand how this treatment approach enhances naming abilities in aphasia, and in turn, for whom rTMS therapy is most likely to have the greatest benefit.

The ability to communicate depends largely on successful word retrieval, the loss of which is a ubiquitous problem in aphasia. Even in single-word production tasks, such as picture naming, people with aphasia are often unable to reliably retrieve the names of common objects. By most accounts, producing a word proceeds in two stages: first the translation of a meaning to its word form (i.e., semantic-to-lexical mapping), followed by the translation of the word to its sound form (i.e., lexical-to-phonological mapping; e.g., Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Levelt, Roelofs, & Meyers, 1999). Because the remediation of word retrieval failures can confer improvements in connected speech (e.g., Hickin, Herbert, Best, Howard, & Osborne, 2002), improving naming abilities is often a focus of aphasia rehabilitation (e.g., Nickels, 2002).

In recent years, a growing body of evidence has shown that rTMS has the potential to enhance naming abilities in chronic post-stroke aphasia (e.g., Barwood et al., 2011, 2012;

Hamilton et al., 2010; Harvey et al., 2017; Naeser et al., 2005a, 2005b). Typically, researchers administer inhibitory rTMS to a region within the right hemisphere homologue of Broca's area, the right pars triangularis (rPtr). For many investigators, this approach is motivated by the view that right hemisphere recruitment in language tasks is maladaptive (e.g., Postman-Caucheteux et al., 2010; Saur et al., 2006; but see e.g., Harvey et al., 2017; Turkeltaub et al., 2012), occurring only as a consequence of an imbalance in transcallosal inhibition between the two hemispheres following damage to the language-dominant hemisphere. According to this *interhemispheric inhibition* hypothesis, left hemisphere damage releases the right hemisphere from transcallosal inhibition, allowing the overactive right hemisphere to suppress recruitment of the already damaged language-dominant hemisphere (Fregni & Pascual-Leone, 2007). Broadly consistent with this hypothesis, inhibitory rTMS to the rPtr or excitatory rTMS to perilesional left hemisphere regions has been shown to increase behaviorally beneficial recruitment of left hemispheric regions during language tasks (e.g., Griffis, Nenert, Allendorfer, & Szaflarski, 2016; Szaflarski et al., 2011). However, it is worth noting that other studies suggest that this may be an oversimplified view of the right hemisphere's role in aphasia recovery (for reviews, see Hamilton et al., 2010; Torres et al., 2013), suggesting instead that in some cases right hemisphere recruitment for language may be compensatory (Chieffo et al., 2014; Turkeltaub et al., 2011, 2012; Winhuisen et al., 2005, 2007). Nevertheless, most accounts agree that rTMS facilitates language recovery by prompting neuroplastic changes in the bilateral neural network recruited for language (e.g., Harvey et al., 2017).

However, due to the relative infancy of rTMS as a treatment for aphasia, the field has yet to establish criteria for determining who is a good candidate for this treatment approach. Prior work has emphasized the highly variable nature of rTMS-induced naming improvements across individuals (e.g., Naeser et al., 2005a; see also Martin et al., 2009a), but the reasons are not well understood. Some studies have demonstrated that, compared to persons with mild aphasia, individuals with moderate-to-severe aphasia exhibit larger gains following rTMS when administered at both the subacute (Seniów et al., 2013) and chronic phases (Barwood et al., 2012; Naeser et al., 2005a; but see Martin et al., 2009a for evidence of no TMS response in a case of global aphasia). Yet, others have found no such relationship between severity and rTMS response (Kindler et al., 2012; Tsai et al., 2014).

Another factor that may impact the extent to which individuals respond to rTMS relates to the processes and stages at which word retrieval becomes impaired due to stroke. Little is known about the specific cognitive processes rTMS alters to facilitate naming performance in aphasia (see e.g., Medina et al., 2012; reviewed in Schwartz, Middleton, & Hamilton, 2015). The characteristics of word retrieval failure in aphasia offer a rich source of information about the underlying cause of naming impairment. For instance, naming performance is in some cases inconsistent, meaning that successful word retrieval for a given item is not always predictive of future retrieval success (e.g., Freed, Marshall, & Chuhlantseff, 1996). Computational models of word retrieval failure account for inconsistent performance by assuming that stroke-related damage increases noise in the production system, where the likelihood of retrieval success for a given item depends on the level of noise that occurs when attempting to access that representation (e.g., Dell et al., 1997; Schwartz et al., 2006; also see Warrington & Cipolotti, 1996; cf. Howard, 1995; Jefferies &

Lambon Ralph, 2006). Accordingly, successful retrieval of a word for which there is some degree of noise will be unreliable, whereas retrieval success for words with elevated noise levels will be unlikely. In addition, erroneous responses typically share a meaning- and/or sound-based relationship with the target response, which provides insight into the stage of processing at which word retrieval fails. Error responses that are semantically similar to the target (e.g., saying “cat” for the picture DOG) arise due to faulty semantic-to-lexical mapping, whereas error responses that are phonologically similar to the target (e.g., saying “log” for the picture DOG) arise due to faulty lexical-to-phonological mapping (Dell et al., 1997; Schwartz et al., 2006; Schwartz, 2014). Understanding where in the production system rTMS facilitates language improvements in people with aphasia may lead to better stratification of patients into rTMS treatment protocols – potentially by identifying who is a good candidate for this neurorehabilitative approach.

1.1. The current study

The present research investigated whether a single session of continuous theta burst stimulation (cTBS) delivered to the rPTr vs. a control site (vertex) confers naming improvements in chronic aphasia, and if so, whether responsiveness to this NIBS technique varies as a function of the severity and/or type of naming impairment. cTBS is an inhibitory form of rTMS that induces robust effects on cortical excitability in a fraction of the time (< 1 minute) required to produce similar effects using low frequency rTMS (e.g., Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). While rTMS studies of aphasia usually involve many days of stimulation to induce enduring effects, we have demonstrated previously that a single session of stimulation can elicit transient benefits in performance (e.g., Hamilton et al., 2010; Harvey et al., 2017). To better understand *for whom* this treatment approach is most likely to benefit, and *how* it may alter cognitive processes to enhance naming abilities, we explored the following three characteristics of aphasic individual’s naming performance: (1) severity of baseline naming impairment; (2) consistency of item-level response accuracy; and (3) the primary locus of naming impairment, as evidenced by the types of errors committed at baseline and their improvement following cTBS. Based on prior work (Barwood et al., 2012; Seniów et al., 2013), we predicted that participants with more severe naming impairments would exhibit larger gains following cTBS of the rPTr vs. vertex when compared to those with less impaired naming abilities. In addition, we hypothesized that items for which retrieval success at baseline was inconsistent would be more likely to improve following cTBS of the rPTr vs. vertex when compared to those that were consistently retrieved unsuccessfully. If true, this would suggest that cTBS enhances naming performance by reducing, rather than eliminating, noise arising during word retrieval.

Lastly, to identify the primary locus of naming failures and the stage at which cTBS enhances performance, we classified all inaccurate responses based on error type. We focused on semantic and phonological errors, as the stages at which these error types arise have been well characterized within cognitive models of word retrieval deficits in aphasia (e.g., Dell et al., 1997; Schwartz et al., 2006). Because the preponderance of NIBS research in aphasia has focused solely on naming accuracy overall, we did not have specific predictions regarding the types of errors this treatment approach targets. If indeed rTMS

confers naming improvements by altering specific cognitive processes that underlie successful word retrieval, we speculated that treatment outcomes might differ depending on where in the system word retrieval fails.

2. Material and methods

2.1. Participants

Eleven participants (9 males) with chronic aphasia due to left hemisphere stroke completed the study protocol (age range = 29–79, mean (M) = 56). All participants were pre-morbidly right-handed (Oldfield, 1971), native English speakers who had suffered a single stroke at least 6 months prior to participation (M = 64.6 months; range = 6–173) (see Table 1). No participant had contraindications to structural magnetic resonance imaging (MRI) or TMS. Informed consent was obtained from all participants in accordance with the IRB of the University of Pennsylvania.

2.2. Lesion data

Lesion location was determined based on high-resolution whole brain structural MRI scans obtained from each participant. Lesions were manually segmented on each participant's T1-weighted structural image by trained technician using MRICron (www.mccauslandcenter.sc.edu/mricron/mricron), and inspected for accuracy by an experienced neurologist – both of whom were blinded to the behavioral data. Normalization of lesion maps to the Montreal Neurological Institute (MNI) space Colin27 template was performed using a symmetric diffeomorphic registration algorithm (Avants, Schoenemann, & Gee, 2006; see also <http://www.picsl.upenn.edu/ANTS/>). Lesion volume and lesion overlap maps were calculated using the VoxBo brain imaging package (<https://github.com/kimberg/voxbo>).

Figure 1 displays a lesion overlap map representing the number of participants with lesions in each voxel. Maximal overlap was localized to the left pars opercularis (POp), or Brodmann area (BA) 44, extending medially to the underlying white matter ($n = 9$). See Table 1 for details regarding lesion location and volume for each participant.

2.3. Clinical data

Participants underwent a battery of neuropsychological assessments to characterize the nature of their impairment. We administered the Western Aphasia Battery (WAB) to classify aphasia subtypes, and obtain a measure of aphasia severity (WAB Aphasia Quotient [AQ]) (Kertesz, 1982). The remaining battery tests assessed picture naming (Roach, Schwartz, Martin, Grewal, & Brecher, 1996), single-word comprehension (Dunn & Dunn, 1997), nonverbal semantic processing (Bozeat et al., 2000; Howard & Patterson, 1992), and apraxia of speech (Dabul, 2000).¹ Of note, percent accuracy on the Philadelphia Naming Test (PNT), a well-characterized test of naming impairment in aphasia (Roach et al., 1996), varied considerably across the group ($M \pm$ standard deviation (SD) = 78.1 ± 14.8 ; range = 43.4–93.1). See Table 1 for participants' demographic and clinical information.

¹Apraxia of speech data were unavailable for one participant (BMP-15).

2.4. rTMS protocol

Stimulation was administered using a 70 mm diameter hand-held figure-of-eight coil (Magstim Super Rapid 2 Plus 1 Transcranial Magnetic Stimulator; Magstim, Whitland, UK). Prior to stimulation, we obtained high-resolution structural MRI scans for each participant. TheBrainsight (Rogue Inc., Montreal, Canada) neuronavigational system was used to mark targets for stimulation (in native space), and co-register structural MRI volumes with respect to the location of the participant and the coil. Participants received cTBS to the rPTr and vertex in separate sessions. The cTBS protocol entailed continuous delivery of 50 Hz triplets of TMS pulses at 5 Hz for a total of 600 pulses (40 seconds). Following prior work, stimulation was delivered at an intensity of 80% of active motor threshold (aMT), as defined using standard methods (see e.g., Huang et al., 2005). The experimental cTBS target was the anterior portion of the right hemisphere homologue of Broca's area, i.e. rPTr (e.g., Naeser et al., 2005a; Barwood et al., 2012). The vertex (control) cTBS target was located at the midline in between primary somatosensory and motor cortices. Stimulation site session order was randomized, with 7 participants receiving rPTr stimulation first and 4 receiving vertex stimulation first.

2.4. Naming measure

2.4.1. Stimuli—Images presented for naming came from the International Picture Naming Project (IPNP) corpus, a standardized set of 520 pictures depicting common objects (Szekely et al., 2004). We initially included all 520 stimuli in the experiment protocol, and later excluded 27 stimuli due to image ambiguity (e.g., picture of a “block” was often confused with “ice cube”) and redundancy (e.g., two pictures depicting different exemplars of the same object, such as “brush”). Excluding these stimuli also served to shorten the baseline naming sessions, and reduce fatigue within a single session.

2.4.2. Design—Participants named pictures in four separate sessions: two baseline and two stimulation sessions. In each of the baseline sessions, participants provided naming responses to the IPNP stimuli, resulting in a total of two responses per item. For each individual, we selected a subset of 160 items for presentation during the stimulation sessions, with the goal that 70% of the stimuli consisted of items named incorrectly in one of the two baseline sessions (inconsistent items) and 30% of the stimuli consisted of items named incorrectly in both sessions (wrong items). Item selection in cases where the desired criterion could not be met precisely ($n = 9$) adhered as closely as possible to the 70/30 ratio of inconsistent/wrong items. The 160 items were divided into four sets of 40 stimuli containing similar proportions of inconsistent and wrong items. The four 40-item sets were matched on factors known to affect lexical access and naming more generally (see e.g., Howard & Gatehouse, 2006; Nickels & Howard, 1995), including lexical frequency, number of syllables, name agreement, objective visual complexity, semantic category membership, and mean naming latency (provided in Szekely et al., 2004).² We then assigned each of the 40-item sets to be presented for naming either before or after cTBS of the rPTr or vertex.

²Note that due to time constraints the 40-item lists were not matched for the types of errors committed on those items at baseline. To reduce the length of time between baseline and stimulation sessions (and in turn minimize the likelihood of losing participants to follow-up testing), trained experimenters conducted a cursory assessment of responses accuracy so as to identify candidate items for

2.4.3. Procedure—In the baseline naming and stimulation sessions, stimuli were presented electronically using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Each trial began with an audio tone that coincided with the presentation of the picture. Naming responses were digitally recorded and later transcribed using the International Phonetic Alphabet (IPA) and coded for accuracy by a trained expert. Experimenters conducting response coding were blinded to the site of stimulation in which responses were collected.

2.4.4. Response coding—Following previously established guidelines (Dell et al., 1997; Roach et al., 1996; Schwartz et al., 2006), we scored the first complete (non-fragment) naming response. Responses were considered correct if they matched the designated target name or referred to the same concept albeit with a different label (i.e., synonym; e.g., trash → garbage). Error types of interest were classified as follows.

Semantic.: Erroneous responses constituting a category coordinate (e.g., dog → cat), superordinate (e.g., dog → animal), subordinate (e.g., dog → poodle), associate (e.g., dog → bone) or multi-word response that describes rather than names the target (e.g., dog → “it goes ‘woof’”). Responses that met the criteria for both semantic and phonological error classification (described below; e.g., dog → frog) were grouped with semantic errors (following Walker et al., 2011; but see Schwartz et al., 2011 for evidence of a neural dissociation between semantic coordinate and associative error production).

Phonological.: Erroneous word and nonword responses with either: (1) one phoneme in common with the target, in the same place (e.g., dog → egg), or (2) two phonemes in common with the target, not necessarily in the same place (e.g., dog → goblet). We computed a measure of phonological overlap for all sound-related errors (i.e., number of phonemes shared between the target and error response divided by the total number of phonemes). Responses with fewer than 75% of phonemes shared with the target word while meeting the above criteria for a phonological error retained the error status within this category, while those with at least 75% overlap were rescored as accurate. This lenient scoring avoided conflating phonological errors with minor speech distortions associated with articulatory-motor deficits (discussed in Schwartz et al., 2006).

Other (unrelated and omissions).: Error responses that did not meet the above criteria for semantic/phonological errors were considered “other errors”. These included both word and nonword responses that bore no semantic and/or phonological relationship with the target (e.g., dog → knife). We also classified as other errors any multiword (description) response that did *not* indicate access to the target’s semantic representation (e.g., dog → “I like that”). Also included in the other category were omission errors (i.e., no response), as defined by the participant indicating verbally or non-verbally that s/he could not name the picture. Lastly, responses in which an entire morpheme was omitted when attempting to name a compound word (e.g., hotdog → dog) were classified as other, rather than phonological, errors because it is highly unlikely that disrupted phonological access would

the stimulation sessions (i.e., those that were inconsistent and wrong across the two baseline sessions). Thus, error classification for baseline naming responses was conducted at the end of the study.

result in the successful retrieval of one morpheme and the omission of the other morpheme. Other errors were not considered to be of interest in the error type analyses (as described in more detail below) since these errors are difficult to localize with respect to the stages of word production that when damaged result in naming failure (e.g., Dell et al., 1997; Schwartz et al., 2006).

2.5. Statistical analyses

We first assessed whether cTBS of the rPTr confers naming improvements for inconsistent and/or wrong items in separate repeated measures analyses of variance (ANOVAs) with accuracy for each item type as the dependent variables. Accuracy was calculated as the percentage of correct responses for each item type out of the total number of items of the same type (inconsistent or wrong) presented in each of the four item lists (pre- vs. post-cTBS of the rPTr vs. vertex). Fixed factors in both analyses included the within-subject variables of Time Point (pre- vs. post-cTBS) and Site (rPTr vs. vertex).

To assess whether response to cTBS differs as a function of baseline naming impairment severity, we assigned participants to two groups based on a median split of baseline naming accuracy, defined as the percentage of items named correctly averaged across the two baselines (following a similar approach implemented in Kindler et al., 2010). We then added the between-subjects factor of Naming Ability (high vs. low) to the repeated measures ANOVAs described above.

Lastly, we explored the relationship between response to cTBS and the locus of word retrieval failure, as determined by the proportion of semantic and phonological naming errors at baseline. Correlational analyses were conducted on the percentage of each error type at baseline and (1) changes in overall naming accuracy from pre- to post-cTBS at each site; and (2) changes in the percentage of each error type from pre- to post-cTBS at each site. Pearson correlations were performed in all analyses except for those involving percentage of semantic errors at baseline, which were performed using Spearman rank correlations due to the non-normal distribution of these values.

3. Results

Analyses at the group level ($n = 11$) revealed that naming accuracy pre- vs. post-cTBS did not differ between rPTr and vertex for either inconsistent or wrong items (p 's $> .41$; see Table 2). However, as expected, individuals varied considerably in their response to cTBS. For inconsistent items, post- minus pre-cTBS naming accuracy (i.e., stimulation effect) ranged from -23.1 to 23.4% following rPTr stimulation, whereas the rPTr-stimulation effect for wrong items ranged from -25.0 to 41.3% . Subsequent analyses assessed whether response to cTBS differed as a function of the severity or locus of naming impairment.

3.1. Naming impairment severity

Across participants, baseline naming accuracy varied considerably ($M = 70.1\%$; range = 37.4 – 93.1% ; see Table 3). A median split of baseline naming accuracy (median = 74.5%) led to the assignment of 5 participants to the *High Naming Ability* group and 6 participants to the *Low Naming Ability* group (Figure 2).

For inconsistent items, Naming Ability significantly interacted with Time Point and Site ($F(1, 9) = 5.92, p = .038$). Follow-up analyses revealed that, compared to individuals with high naming ability, naming performance among those with low naming ability improved following cTBS of the rPTr and not vertex. By contrast, individuals with high, as compared to low, naming ability performed worse following rPTr, but not vertex, stimulation (Figure 3a). However, in the analysis of wrong items, Naming Ability did *not* significantly interact with Time Point and Site ($F(1, 9) = 1.54, p = .25$), as pre-/post-cTBS performance changes did not differ for individuals with low vs. high naming ability following cTBS to either site (Figure 3b). See Table 4 for follow-up analyses test statistics. Individual participant data are provided as Supplementary material.

Consistent with previous research (Barwood et al., 2012; Naeser et al., 2005b; Seniów et al., 2013), these findings provide some evidence indicating that rTMS outcomes differ depending on baseline naming impairment severity. However, contrary to what might be expected, severity was *not* significantly correlated with improved naming of inconsistent items following rPTr stimulation ($r = -.08, p = .81$; Figure 4a) or vertex stimulation ($r = .18, p = .60$; Figure 4b) across all participants ($n = 11$). This suggests that overall severity may not be a sensitive enough measure to explain variation in individual's response to cTBS. To explore whether the type of naming impairment relates to rTMS outcomes, we conducted correlational analyses between error profiles at baseline and cTBS response for inconsistent items only.

3.2. Error type

At baseline, the percentage of semantic ($M = 13.8\%$; range = 4.0–39.5%) and phonological errors ($M = 7.4\%$; range = 1.3–16.9%) also varied considerably across participants (Table 3). We found a weak – albeit non-significant – relationship between semantic naming impairment at baseline and overall naming improvements following rPTr stimulation ($\rho = -.56, p = .08$), where individuals with more severe semantic naming impairment tended to perform worse following stimulation (Figure 4c). However, baseline semantic naming impairment was neither correlated with changes in naming accuracy following vertex stimulation ($\rho = -.17, p = .61$; Figure 4d) nor with changes in semantic error production following stimulation to either site (ρ 's $< .42, p$'s $> .26$; Figures 5a and 5b). By contrast, severity of baseline phonological naming impairment was marginally correlated with overall naming improvements ($r = .59, p = .057$; Figure 4e), and significantly correlated with fewer phonological errors following cTBS of the rPTr ($r = -.63, p = .04$; Figure 5c). Critically, phonological errors were not related to performance changes following vertex stimulation (r 's $< .21, p$'s $> .56$; Figures 4f and 5d). Together, our data suggests that, when cTBS of the rPTr is associated with improved naming for retrieval failures, that benefit represents reduced failures in phonological access, rather than a reduction in retrieval failures more generally.

4. Discussion

We investigated the cognitive mechanism(s) by which rTMS enhances naming abilities in individuals with chronic post-stroke aphasia by exploring whether the degree and/or primary

source of naming impairment was associated with individuals' responsiveness to this treatment approach. Our findings indicate that cTBS of the rPTr enhances naming abilities for individuals with more severe baseline naming impairment when naming objects for which they could retrieve successfully – albeit inconsistently – at baseline. Interestingly, however, baseline naming impairment severity more generally was not correlated with cTBS-induced naming improvements across the group, despite the finding that high naming ability participants' performance decreased on average and low naming ability participants' performance increased on average following cTBS to the rPTr. Instead, we found that the primary locus of naming impairment related to individuals' responsiveness to cTBS, whereby the extent of phonological access impairment at baseline marginally correlated with naming improvements overall and significantly correlated with decreased error responses arising at the stage of phonological retrieval following cTBS of the rPTr. By contrast, semantic error production was not related to cTBS effects, as the severity of lexical-semantic access impairment at baseline was not significantly associated with cTBS-induced naming improvements. Thus, the current study provides insight into which specific aspects of language difficulties cTBS targets when administered to the rPTr, indicating that rTMS enhances naming performance at the level of phonological access.

To date, the cognitive mechanism(s) by which rTMS enhances naming performance have received little attention in neurorehabilitation studies assessing the clinical utility of this treatment approach in remediation of word retrieval impairments in aphasia. To our knowledge, only one prior study employed an item selection protocol similar to that used in the current study, though this study did not assess whether rTMS differentially affected performance for items named incorrectly in one or both of the baseline sessions (i.e., inconsistent vs. wrong items; Chieffo et al., 2014). No prior study has investigated response error profiles as it relates to rTMS-induced naming improvements. By examining the types of items and error response profiles that respond to rTMS therapy, the current study provides insight into the mechanisms by which rTMS enhances naming. That cTBS enhanced phonological access for items in which participants were unable to reliably retrieve successfully at baseline indicates that this treatment approach may facilitate naming abilities in aphasia by increasing the signal-to-noise ratio at the level of lexical-to-phonological mapping (e.g., Dell et al., 1997; also see Warrington & Cipolotti, 1996), rather than decreasing noise arising at other levels of production system.

It is worth noting, however, that items retrieved unsuccessfully across both baseline sessions were named correctly prior to cTBS of the rPTr and in the vertex session, which is consistent with the view that word retrieval is a probabilistic event in which the level of noise affects the likelihood of retrieval success (e.g., Dell et al., 1997; Schwartz et al., 2006). Assuming that retrieval success in one out of two vs. three attempts signifies less noise, the finding that improvements occurred only for items retrieved successfully in at least one of the baseline sessions may suggest that rTMS is best suited for treating naming impairment when the amount of noise is below some threshold. Moreover, it could be argued that the findings are not indicative of cTBS improving noisy phonological access, but instead reflect an inherent relationship between the consistency of response accuracy and phonological error production – at least in this patient sample. However, comparisons between the rates of semantic and phonological errors committed on inconsistent items at baseline suggest that

this is not the case (i.e., $M_{\text{phonological}} = 3.96\%$ vs. $\text{semantic} = 4.17\%$; $t(10) = .19$, $p = .85$). Lastly, that inconsistent items did not improve following vertex stimulation argues against the possibility that improvements for these items following rPTr stimulation occurred by chance.

Why does rTMS facilitate phonological access, and not other stages of the production system? One plausible explanation relates to the site of stimulation. The rPTr is often the target for inhibitory rTMS protocols due to its presumed maladaptive role in aphasia recovery (Naeser et al., 2005a). Behavioral improvements following rPTr inhibition (and other therapies) are associated with a posterior shift in the recruitment of regions within Broca's area homologue (e.g., Harvey et al., 2017; also see Crosson et al., 2009), namely the right pars opercularis (rPOp). The rPOp, but not the rPTr, is thought to be functionally homologous to its left hemisphere counterpart (e.g., Turkeltaub et al., 2011). Importantly, in the left hemisphere, the POp and the PTr subserve functionally dissociable roles in phonological and semantic processes, respectively (e.g., Gough et al., 2005; also see Halai et al., 2017). Speculatively, this could suggest that inhibiting rPTr confers naming improvements by prompting behaviorally beneficial recruitment of the rPOp, resulting in enhanced phonological access.

An alternative – albeit not mutually exclusive – explanation for the current findings is that cTBS-induced naming improvements manifesting in improved phonological access reflect remediation of motor-speech deficits observed in apraxia of speech. It is notoriously difficult to distinguish between anomic and apraxic sources of sound-related speech errors (e.g., Haley, Jacks, & Cunningham, 2013). In the current study, we adopted a lenient criterion for scoring responses phonologically similar to the target as correct (i.e., responses with at least 75% phonological overlap with the target were coded as correct). However, it may still be the case that for some individuals, phonological errors that did not meet this lenient threshold for accuracy were apraxic in nature. Indeed, of the six individuals with more severe naming impairment at baseline, five presented with apraxia of speech, which is in contrast to the four high naming ability individuals who underwent diagnostic testing for apraxia of speech and showed no signs of this impairment. This could suggest that the mechanism supporting naming improvement following rPTr inhibition may in part be localized to speech-motor deficits thought to be the primary source of impairment in apraxia of speech (e.g., Basilakos, Rorden, Bonilha, Moser, & Fridriksson, 2015). Future work is needed to disentangle improvements in phonological access and/or motor speech production following inhibition of the rPTr.

4.1. Limitations

Despite these promising results, there are some limitations to this study that warrant discussion. First, the moderate sample size consisting of individuals with varying clinical profiles may affect the generalizability of our findings. However, there are several features of our design that militate against certain concerns. The inclusion of two baseline sessions and an individualized item selection protocol make it unlikely that the cTBS effects reported here were due to learning effects and/or baseline differences in item-level naming abilities (Freed et al., 1996). Moreover, given that our main finding speaks to individual differences

in rTMS effects, the heterogeneity of this patient sample may, in fact, be advantageous for uncovering the factors that drive variable rTMS-induced naming improvements. Second, the effect sizes reported here are relatively small when compared to those obtained in studies administering multiple days of rTMS therapy (e.g., Tsai et al., 2014); however, they are similar to a previous report of single-session cTBS effects (Kindler et al., 2012). Critically, when considered alongside our finding that the degree of recovery following cTBS of the rPTr depends on the type of naming impairment prior to treatment – with larger treatment effects for individuals with greater phonological access deficits – this suggests that the relatively weak group-level effects may stem from variability in the types of naming impairment among this patient sample. Thus, it may be possible to obtain larger effect sizes if the types of errors elicited by each item at baseline were considered during the selection of items presented during stimulation – a design feature that we were unfortunately unable to implement due to time constraints, but is an important consideration for future work. Finally, although the present research cannot directly speak to the underlying *neural* mechanisms that enable improved phonological access following rTMS therapy – as we did not concurrently collect functional neuroimaging data – these findings have important implications for understanding the specific cognitive and linguistic processes that are modified by the application of stimulation at a site that is a frequent target in rTMS studies of aphasia, and potentially provide insight into which patients are most likely to benefit from interventions that manipulate this anatomic site. In future work, it will be important to replicate and extend these findings in a larger cohort of patients using different stimulation protocols in combination with functional neuroimaging techniques.

5. Conclusion

To our knowledge, this is the first study to examine the characteristics of naming impairment in aphasia as it relates to variable rTMS treatment outcomes. The findings from this research not only lay the groundwork for incorporating cognitive models of word retrieval failure in future studies of rTMS in aphasia, but they also have the potential to inform the stratification of patients into effective rTMS protocols. In the current study, we provide evidence that individuals with word retrieval deficits localized to phonological access may be optimal candidates for rTMS treatment protocols involving inhibitory stimulation of the rPTr.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of significance

This research points to phonological processing as a specific cognitive-linguistic ability that is enhanced in persons with chronic post-stroke aphasia who undergo TMS therapy. By clarifying which aspects of word retrieval improve following TMS, this work has the potential to inform optimal stratification of patients in TMS treatment protocols.

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Figure 1. Maps displaying lesion overlaps for the 11 participants within the left hemisphere. Maximal lesion overlap (depicted in dark red) was localized to the left pars opercularis (POp), or BA 44, where 9 out of 11 participants had damage to this region extending medially. Sagittal, coronal, and axial slices are at MNI xyz coordinates of -43, 5, and 20.

Figure 2.

Percentage of correct responses averaged across the two baseline naming sessions. Striped bars denote individuals assigned to the Low Naming Ability group, whereas solid bars denote individuals assigned to the High Naming Ability group (based on median split). Individuals are arranged in order from lowest to highest baseline naming accuracy.

Figure 3. Mean stimulation effect (post- minus pre-cTBS) on naming accuracy and associated within-subjects 95% confidence intervals separated by Naming Ability for (a) inconsistent items and (b) wrong items. An “*” indicates a significant effect at $p < .05$.

Figure 4.

Scatter plots depicting the relationships between measures of baseline naming impairment severity and the stimulation effect (post- minus pre-cTBS) following cTBS of the rPTr and vertex. (a-b) Correlations between baseline naming impairment severity (i.e., Baseline Accuracy) and the stimulation effect at each site. (c-d) Correlations between baseline semantic naming impairment (i.e., Baseline Semantic Errors) and the stimulation effect at each site. (e-f) Correlations between baseline phonological naming impairment (i.e., Baseline Phonological Errors) and the stimulation effect at each site. A “†” indicates a significant effect at $p < .10$.

Figure 5.

Scatter plots depicting the relationship between (a-b) baseline semantic naming impairment (i.e., Baseline Semantic Errors) and the stimulation effect (post- minus pre-cTBS) on semantic error production; and (c-d) baseline phonological naming impairment (i.e., Baseline Phonological Errors) and the stimulation effect on phonological error production following cTBS of the rPTr and vertex. An “*” indicates a significant effect at $p < .05$.

Table 1

Participant Demographics and Neuropsychological Characteristics

Patient	Gender	Age	Ed	MPO	WAB AQ	Aphasia Subtype	PNT %Acc	PPVT Stand Score	PPT %Acc	CCT %Acc	Speech Apraxia	Lesion Vol (cc)	Lesion Distribution
BMP-01	M	51	14	63	83.2	Anomic	85.1	66	92	77	No	61.36	L frontal (BA 44, 45, & 47), insula, & M1
BMP-06	M	79	21	89	80.8	Anomic	93.1	100	96	83	No	51.96	L parietal, pMTG & pSTG
BMP-08	M	57	14	111	77.8	Broca's	82.3	87	94	89	Yes	172.29	L frontal (BA 44, 45, & 47), insula, M1, S1, IPL & pSTG
BMP-09	M	51	12	26	77.0	Broca's	85.1	84	94	80	Yes	89.60	L frontal (BA 44 & 45), insula, M1, S1, IPL & pSTG
BMP-10	M	68	19	173	48.4	Broca's	43.4	81	92	78	Yes	282.64	L frontotemporoparietal
BMP-11	M	37	14	6	71.6	Conduction	79.4	92	100	80	Yes	88.00	L frontal (BA 44), insula, & temporal lobe (sparing ITG)
BMP-15	M	56	16	8	87.3	Anomic	91.4	105	96	84	NA	23.86	L frontal (BA 44 & 45) & insula
BMP-19	M	29	14	43	89.2	Anomic	82.3	90	94	83	No	421.00	L frontotemporoparietal
BMP-24	F	47	16	156	86.8	Anomic	87.4	81	94	72	No	209.69	L frontal (BA 44, 45, & 47), insula, M1, S1, aMTG, & aSTG.
BMP-26	M	70	18	25	84.5	Anomic	64.0	96	98	89	No	57.47	L IPL, S1, aSTG & occipital lobe (sparing IOG)
BMP-28	F	66	10	11	67.2	Broca's	65.1	73	88	77	Yes	56.16	L frontal (BA 44), IPL, M1, & S1
Mean		55.5	15.3	64.6	77.6		78.1	86.8	94.5	81.0		137.64	
Range		29–79	10–21	6–173	48.4–89.2		43.4–93.1	66–105	88–100	71.8–89.0		23.9–421.0	

Note. Aphasia subtype and severity (i.e., WAB AQ) were evaluated using the Western Aphasia Battery (WAB), where lower AQ values signify greater severity (Kertesz, 1982). The Philadelphia Naming Test (PNT) (Roach et al., 1996) served as an independent measure of baseline naming ability, where scores are expressed as percent correct. Standard scores are reported for the Peabody Picture Vocabulary Test—III, a standardized measure of single word comprehension, where a score of 100 reflects the (normal) mean and 15 points represent a standard deviation (Dunn & Dunn, 1997). Nonverbal semantic processing was assessed using two tests of associative picture-picture matching – the Pyramids and Palm Trees test (Howard & Patterson, 1992) and Camel and Cactus Test (Bozeat et al., 2000). Speech Apraxia was evaluated with the Apraxia Battery for Adults-Second Edition (ABA-2) (Dabul, 2000); ABA-2 data were unavailable for one participant. Ed = years education, MPO = months post-stroke onset, WAB AQ = Western Aphasia Battery Aphasia Quotient, PNT = Philadelphia Naming Test, %Acc = percent accuracy, PPVT = Peabody Picture Vocabulary Test, StandScore = standardized score, PPT = Pyramids and Palm Trees test, CCT = Camel and Cactus Test, NA = not available, vol = volume, cc = cubic centimeters, L = left, BA = Brodmann area, M1 = primary motor cortex, S1 = primary somatosensory cortex, pMTG = posterior middle temporal gyrus, pSTG = posterior superior temporal gyrus, aMTG = anterior middle temporal gyrus, aSTG = anterior superior temporal gyrus, ITG = inferior temporal gyrus, IPL = inferior parietal lobule, IOG = inferior occipital gyrus.

Table 2

Repeated Measures ANOVA Results on Naming Accuracy at the Group-level (n =11) for the Site by Time Point Interaction Separated by Item Type

	$F_{(1,10)}$	p	rPTr $M \pm SD$	Vertex $M \pm SD$
Inconsistent	0.18	0.65	$-1.6 \pm 14.1\%$	$-3.9 \pm 10.7\%$
Wrong	0.72	0.42	$-1.5 \pm 20.1\%$	$4.6 \pm 21.3\%$

Note. Mean (M) $\pm$ standard deviation (SD) reflects the post- minus pre-cTBS difference in naming accuracy per item type (i.e., inconsistent and wrong) at each stimulation site (i.e., rPTr and vertex). F = F statistic, p = p value, rPTr = right pars triangularis.

Table 3

Baseline Naming Accuracy and Percentage of Semantic and Phonological Errors

Subject ID	Item Type			Response Type		
	Correct	Inconsistent	Wrong	Correct	Semantic	Phonological
BMP-01	65.6	18.5	16.0	74.8	15.2	3.1
BMP-06	70.4	15.0	14.6	77.9	11.8	4.8
BMP-08	57.1	26.0	16.9	70.1	8.4	15.9
BMP-09	60.7	27.5	11.8	74.5	10.0	7.0
BMP-10	27.4	20.7	51.9	37.4	39.5	7.9
BMP-11	49.4	25.8	24.8	62.3	14.5	5.2
BMP-15	89.5	7.3	3.2	93.1	4.0	1.3
BMP-19	66.5	18.6	14.9	75.9	14.4	1.3
BMP-24	71.2	16.8	12.0	79.6	11.0	1.9
BMP-26	52.5	34.3	13.2	69.7	9.1	16.3
BMP-28	42.4	27.6	30.0	56.2	13.6	16.9
Mean	59.3	21.6	19.0	70.1	13.8	7.4
Range	27.4–89.5	7.3–34.3	3.2–51.9	37.4–93.1	4.0–39.5	1.3–16.9

Note. Item type values reflect the percentage of items out of the total number of items presented that were named accurately in both baseline sessions (Correct), in one of the two baseline sessions (Inconsistent), or in neither of the baseline sessions (Wrong). Response type values reflect the percentage of trials out of the total number of trials combined across the two baseline sessions in which a response was accurate (Correct), bore a meaning-based relationship with the target response (Semantic) or a sound-based relationship with the target (Phonological).

Table 4

Results of the Independent Samples T-tests Comparing Pre-/Post-cTBS Naming Accuracy for Low vs. High Naming Ability Groups Separated by Site and Item Type

	$t_{(9)}$	p	Low Naming Ability $M \pm SD$	High Naming Ability $M \pm SD$
rPTr				
Inconsistent	-2.80	0.02	$6.8 \pm 12.0\%$	$-11.6 \pm 9.3\%$
Wrong	0.06	0.95	$1.8 \pm 17.6\%$	$-1.0 \pm 25.0\%$
Vertex				
Inconsistent	0.51	0.62	$-5.4 \pm 10.8\%$	$-2.0 \pm 11.5\%$
Wrong	1.50	0.17	$-3.7 \pm 26.1\%$	$14.6 \pm 7.2\%$

Note. Mean (M) $\pm$ standard deviation (SD) reflects the post- minus pre-cTBS difference in naming accuracy per item type (i.e., inconsistent and wrong) at each stimulation site (i.e., rPTr and vertex). t = t statistic, p = p value, rPTr = right pars triangularis.