Aphasiology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/paph20

Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke

Jared Medina [a], Catherine Norise [b], Olufunsho Faseyitan [a], H. Branch Coslett [a], Peter E. Turkeltaub [b] & Roy H. Hamilton [a]

[a] Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

[b] Department of Neurology, Georgetown University, Washington, DC, USA

Version of record first published: 29 Aug 2012.

To cite this article: Jared Medina, Catherine Norise, Olufunsho Faseyitan, H. Branch Coslett, Peter E. Turkeltaub & Roy H. Hamilton (2012): Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke, Aphasiology, 26:9, 1153-1168

To link to this article: http://dx.doi.org/10.1080/02687038.2012.710316

APHASIOLOGY, 2012, 26 (9), 1153–1168

Psychology Press
Taylor & Francis Group

Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke

Jared Medina[1], Catherine Norise[2], Olufunsho Faseyitan[1], H. Branch Coslett[1], Peter E. Turkeltaub[2], and Roy H. Hamilton[1]

[1]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Neurology, Georgetown University, Washington, DC, USA

Background: Loss of fluency is a significant source of functional impairment in many individuals with aphasia. Repetitive transcranial magnetic stimulation (rTMS) administered to the right inferior frontal gyrus (IFG) has been shown to facilitate naming in persons with chronic left hemisphere stroke and non-fluent aphasia. However, changes in fluency in aphasic participants receiving rTMS have not been adequately explored.
Aims: To determine whether rTMS improves fluency in individuals with chronic nonfluent aphasia, and to identify aspects of fluency that are modulated in persons who respond to rTMS.
Methods & Procedures: Ten individuals with left hemisphere MCA strokes and mild to moderate non-fluent aphasia participated in the study. Before treatment participants were asked to describe the Cookie Theft picture in three separate sessions. During treatment all participants received 1200 pulses of 1 Hz rTMS daily in 10 sessions over 2 weeks at a site that had previously been shown to improve naming. Participants repeated the Cookie Theft description 2 months after treatment. Five participants initially received sham stimulation instead of real TMS; 2 months after sham treatment these individuals received real rTMS. Performance both at baseline and after stimulation was coded using Quantitative Production Analysis (Saffran, Berndt, & Schwartz, 1989) and Correct Information Unit (Nicholas & Brookshire, 1993) analysis.
Outcomes & Results: Across all participants ($n = 10$), real rTMS treatment resulted in a significant increase in multiple measures of discourse productivity compared to baseline performance. There was no significant increase in measures of sentence productivity or grammatical accuracy. There was no significant increase from baseline in the sham condition ($n = 5$) on any study measures.
Conclusions: Stimulation of the right IFG in patients with chronic non-fluent aphasia facilitates discourse production. We posit that this effect may be attributable to improved lexical-semantic access.

Keywords: Language; Aphasia; Transcranial magnetic stimulation; TMS; Pars triangularis; Fluency; Neurorehabilitation.

Address correspondence to: Roy H. Hamilton, MD, MS, Goddard Laboratories, Room 518, University of Pennsylvania, 3710 Hamilton Walk, Philadelphia, PA 19104, USA. E-mail: Roy.Hamilton@uphs.upenn.edu

Sources of funding: HBC: NIH 2R01 DC05672-04A2. RHH: NIH/NINDS 1K01NS060995-01A1. RHH: Robert Wood Johnson Foundation/Harold Amos Medical Faculty Development Program. PET: American Academy of Neurology Foundation.

http://www.psypress.com/aphasiology http://dx.doi.org/10.1080/02687038.2012.710316

Failure of spontaneously generated fluent speech is a source of considerable disability for many individuals with aphasia after stroke, particularly those with anterior lesions of the left hemisphere. Nonfluent aphasia is typically characterised by difficulties in speech output, with deficits including interrupted speech, word omission, loss or misuse of inflectional morphology, and utterances with limited syntactic complexity. However, depending on lesion size and location, different individuals may experience a variety of specific impairments to varying degrees, including but not limited to deficits in speech initiation, poor retrieval of accurate semantic or lexical representations, disrupted sequencing of articulatory movements, or inaccurate grammatical constructions (Gleason, Goodglass, Green, Ackerman, & Hyde, 1975; Kolk & Heeschen, 1990).

Recent studies have suggested that exogenous manipulation of cortical activity with repetitive transcranial magnetic stimulation (rTMS) may improve naming in persons with chronic left hemisphere stroke and nonfluent aphasia (e.g., Barwood et al., 2011; Martin et al., 2009; Naeser et al., 2005; Weiduchat et al., 2011; and others). Most investigations in this area have employed low-frequency (1Hz) inhibitory rTMS of the right inferior frontal gyrus (RIFG), and within that region many studies have focused on the right pars triangularis (RPTr). The specific mechanisms by which rTMS administered to this region produces beneficial changes in language ability are debated. Proposed mechanisms have included the dampening of inhibitory transcallosal connections between the right and left hemispheres or modification of intrahemispheric connections within a compensatory network of right hemisphere language areas (see Hamilton, Chrysikou, & Coslett, 2011 for a review of this topic).

To date most studies investigating the effects of rTMS on language recovery in patients with chronic nonfluent aphasia have focused on changes in naming ability. Naeser and colleagues (2005) reported improved performance on the Boston Naming Test and naming subtests of the Boston Diagnostic Aphasia Examination in four participants who received 1Hz rTMS to the RIFG for 10 days (see also Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009). Investigators have used transient changes in naming ability after single sessions of 1Hz rTMS as a strategy for identifying optimal stimulation targets within right inferior frontal gyrus in nonfluent aphasic individuals (Hamilton et al., 2010; Naeser et al., 2011; Turkeltaub, Coslett, et al., 2011).

Despite the impact of dysfluency on the functional abilities of many individuals with nonfluent aphasia, relatively little has been reported with regard to the effect of right hemisphere rTMS on this aspect of language. To date only three studies have reported spontaneous speech data in individuals who have undergone right hemisphere rTMS treatment. These studies have reported the greatest number of words in a phrase (Barwood et al., 2011; Martin et al., 2009; Naeser et al., 2005), articulatory agility (Naeser et al., 2005), or picture description complexity index (Barwood et al., 2011) as dependent variables. However, detailed coding schemes, like Quantitative Production Analysis (QPA; Rochon, Saffran, Berndt, & Schwartz, 2000; Saffran et al., 1989), can be used to fully characterise the various dissociable aspects of language production that contribute to fluent spontaneous speech. After coding spontaneous speech, past experimenters have found that specific variables in speech production in aphasics tend to correlate. For example, Rochon and colleagues (2000) found that a three-factor model (sentence structure, unbound morpheme frequency, speech rate) characterised performance in a set of 37 aphasic individuals. Others have grouped measures from QPA into categories based on various aspects of language (Gordon, 2006).

We examined whether right IFG rTMS treatment changed narrative speech production in a group of nonfluent aphasic participants using QPA and by tallying Correct Information Units (CIUs), a measure of the semantic content of participants' utterances (Nicholas & Brookshire, 1993). By identifying the specific aspects of spontaneous speech that are altered as a result of stimulation, we aimed to provide further insight into the specific linguistic processes improved by TMS.

METHOD

Participants

A total of 10 participants (3 female) ranging in age between 47 and 75 years (mean ± *SD*, 61.60 ± 8.32) took part. All participants had sustained a single left hemispheric unilateral ischaemic stroke (Figure 1) and were classified as having mild to moderate nonfluent aphasia by Boston Diagnostic Aphasia Examination tests (BDAE; Goodglass, Kaplan, & Barresi, 2001) administered at the initial screening. To be eligible for the study patients must have been able to produce meaningful words as well as phrases between 2–4 words in length during their baseline language evaluation. To ensure that participants were able to cooperate during testing they also must have had relatively intact language comprehension, operationally defined by performance at or above the 25th percentile on the BDAE subtests for word comprehension and commands. Additionally participants must have been able to name at least 3 items of the first 30 on the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001) and an average of at least 3 pictures out of 20 when presented with 10 sets of picture naming stimuli taken from the Snodgrass and Vanderwart corpus (1980). All participants were at least 6 months post-stroke, had no other concurrent history of neurological or psychiatric disease or unstable medical conditions, and had no contra-indications to either MRI or TMS. The study was approved by the Institutional Review Board of the University of Pennsylvania, and all participants provided informed consent. Additional participant demographic, baseline performance, and lesion data are provided in Table 1.

STUDY OVERVIEW

At the start of the study all participants underwent baseline language assessment three times on average (range: 1–4). The baseline assessment included testing with

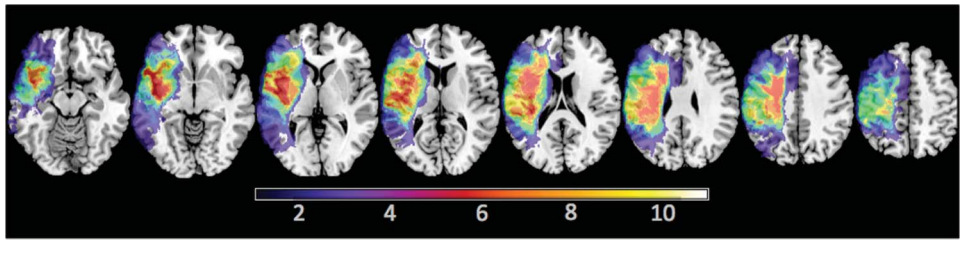

Figure 1. Lesion overlap for all 10 left MCA stroke participants mapped onto the Colin27 MNI template. The location of maximal overlap (bright orange) includes the left insula, Heschl's gyrus, and Rolandic operculum. To view this figure in colour, please see the online issue of the journal.

TABLE 1
Demographics, lesion descriptions, and aphasia severity measures for study participants

							Aphasia Severity		
Subject	*Sex*	*Age, y*	*Education, y*	*Time Since Stroke, mo*	*Lesion Distribution*	*Lesion Volume, cm^3*	*Phrase length (BDAE), mean*	*Naming ability (BNT), (maximum 30)*	*Auditory Comprehension-Commands (BDAE), (maximum 15)*
					Real TMS				
1	M	60	18	87	Large MCA cortical and subcortical, including BA 44, 45, & 47	252.11	2.5	21	8
2	M	61	18	63	Large MCA cortical and subcortical, including BA 44, 45, & 47	130.91	2	7	14
3	M	51	14	45	Fronto-pariental cortical and subcortical, including interanal capsule, basal ganglia, BA 44, 45, & 47	134.03	3.5	27	15
4	F	71	18	48	Fronto-temporo-parietal subcortical greater than cortical, including internal capsule, basal ganglia & thalamus; M1 & IFG spared	91.65	5	20	11
5	M	60	24	6	Small fronto-temporo-parietal cortical and subcortical; minor involvement of corona radiata; IFG and insula spared	36.59	3	8	15
	Mean (StdDev)	60.6 (±7.1)	18.4 (±3.6)	49.8 (±29.6)		129.1 (±79.2)	3.2 (±1.2)	16.6 (±8.7)	12.6 (±3.0)

(*Continued*)

TABLE 1
(Continued)

							Aphasia Severity		
Subject	*Sex*	*Age, y*	*Education, y*	*Time Since Stroke, mo*	*Lesion Distribution*	*Lesion Volume, cm³*	*Phrase length (BDAE), mean*	*Naming ability (BNT), (maximum 30)*	*Auditory Comprehension-Commands (BDAE), (maximum 15)*
					Sham TMS				
1	M	65	12	29	Subcortical, including corona radiata, internal capsule, basal ganglia, & thalamus; IFG spared	53.02	2.5	13	11
2	F	65	16	20	Large MCA cortical & subcortical, including BA 44, 45, & 47	201.62	3	20	8
3	M	47	12	102	Cortical & subcortical, including internal capsule, basal ganglia, thalamus, M1, and BA 44; BA 45 & 47 spared	123.83	2.5	26	11
4	F	61	14	59	Large MCA cortical & subcortical, including BA 44, 45, & 47	178.99	1	17	14
5	M	75	18	83	Fronto-temporo-parietal subcortical, including corona radiata but sparing internal capsule and deep grey structures; IFG spared	118.49	3	21	11
	Mean (StdDev)	62.6 (±10.1)	14.4 (±2.6)	58.6 (±34.8)		135.2 (±58.1)	2.4 (±0.8)	19.4 (±4.8)	11.0 (±2.1)

the Cookie Theft Picture Description subtest of the BDAE, described further below. The average interval between initial and final baseline testing sessions was 33 days ($SD = 34.16$ days). Following baseline assessment each participant was randomised into one of two groups: One group ($n = 5$) received real rTMS while the other group ($n = 5$) initially received sham stimulation (sTMS). Statistically these two groups did not differ significantly with respect to age, lesion size, time since stroke onset, or initial measures of aphasia severity. There was a trend towards significance between the two groups with respect to years of education, $t(7.3) = 2.02$; $p = .081$, with a greater number of years of education in the rTMS group (18.4, $SD = 3.6$) than the sham group (14.4, $SD = 2.6$). Participants receiving real rTMS underwent a series of six sessions of rTMS applied to different sites in right IFG in order to identify the optimal target for stimulation. After an optimal site was identified for each individual participant, stimulation was administered to that site in 10 sessions over 12 days (daily sessions occurred Monday through Friday for 2 weeks with no stimulation on Saturday or Sunday), as described below. Participants subsequently completed a follow-up language assessment including Cookie Theft Picture Description 2 months following the completion of stimulation. Testing was not pursued immediately after discontinuation of stimulation because of concerns that repeating language tasks only a short interval after finishing baseline testing might elicit practice effects. Prior evidence (Hamilton et al., 2010) suggested that improvements in spontaneous speech due to rTMS could be observed after 2 months. Participants randomised to the sham group received sham rTMS during both the optimal target identification phase of the study as well as during the 10-session treatment phase. These participants completed a follow-up language assessment including the Cookie Theft Picture Description 2 months following sTMS, and subsequently crossed over into the real rTMS arm of the study, such that all participants in the study eventually received real rTMS. Study events are summarised in Figure 2.

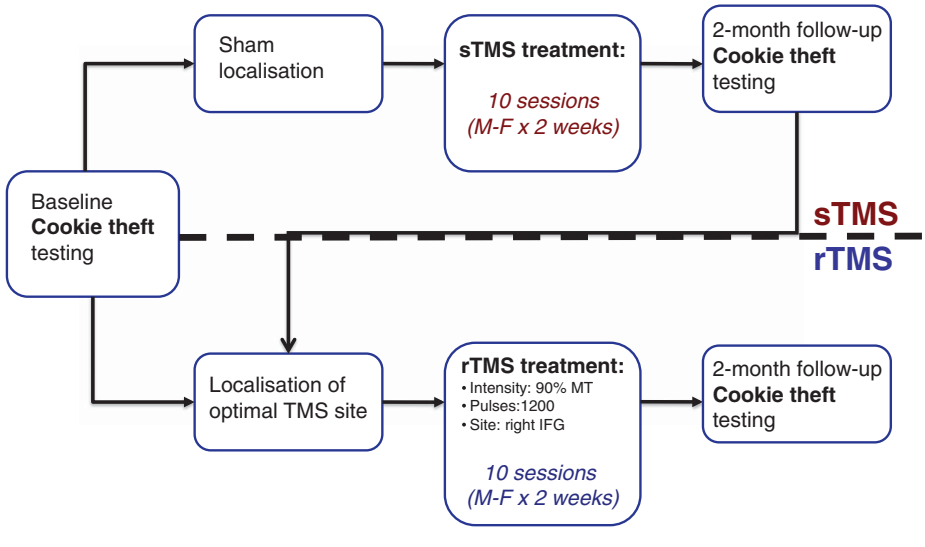

Figure 2. Outline of study events.

rTMS methods

Stimulation was administered with a Magstim Rapid transcranial magnetic stimulator, connected to a 70-mm diameter figure-of-eight coil (Magstim, Whitland, UK). A 3.0 Tesla Siemens Trio Scanner was used to collect high-resolution whole-brain T1-weighted images for each participant. The Brainsight system (Rogue Research, Montreal) was used to co-register MRI data with the location of the participant and coil in both phases of the study. The participant's resting motor threshold (RMT) was established according to published criteria (Rossini et al., 1994). Sham TMS was administered using the same setup, but with the coil perpendicular to the head so that only the rim of the coil contacted the head. During real stimulation the coil was oriented with the handle in a posterior and inferior direction approximately 45 degrees clockwise from the downward position. Real rTMS was delivered at an intensity of 90% RMT and a frequency of 1 Hz. During each of the 10 sessions of the treatment phase of the study participants in the real rTMS arm of the study received 1200 pulses of 1Hz rTMS at 90% RMT; participants in the sham arm 1200 pulses of sTMS.

Identification of optimal stimulation site

These methods are described in more detail elsewhere (Hamilton et al., 2010; Naeser et al., 2011). In six separate sessions conducted over 5 days (two sessions were conducted on the last day) different sites in the right inferior frontal lobe were stimulated with rTMS. During these sessions participants in the real rTMS arm of the study received 600 pulses of 1Hz rTMS at an intensity of 90% RMT, while participants in the sham arm received 600 pulses of sTMS. Sites included the region of the motor cortex corresponding to the mouth, a site on pars opercularis (BA 44), three separate sites on the pars triangularis (BA 45; designated in this study as the dorsal posterior, ventral posterior, and anterior pars triangularis), and the pars orbitalis (BA 47). Prior to and immediately following rTMS at each candidate site, participants performed a 40-item picture-naming task. As in previous work, responses that differed from the target by one phoneme were counted as correct (e.g., Naeser et al., 2005). As previously reported, a site was considered to be the optimal target for stimulation if a participant showed the greatest increase in naming accuracy after stimulation of that target and if the change in naming accuracy observed after stimulation of that target was greater than two times the standard deviation of the mean pre-stimulation performance across all sites (Hamilton et al., 2011). Consistent with prior investigations, for 9 out of 10 participants tested, the optimal site was in the right pars triangularis (RPTr); for one participant the optimal site was found to be in the right pars orbitalis (see Figure 3).

Stimulus presentation

Seated comfortably in a quiet testing environment, participants were presented with the "Cookie Theft" picture from the Boston Diagnostic Aphasia Examination by an examiner, and instructed to report everything they saw in the picture. Examiner interruptions were limited to general prompts (e.g., "what's happening here"); examiners did not point to or allude to specific content in the picture. There was no time limit for responses. Participants performed this task three times at baseline and after 2-month real rTMS follow-up. Participants randomised to the sham arm performed the task at

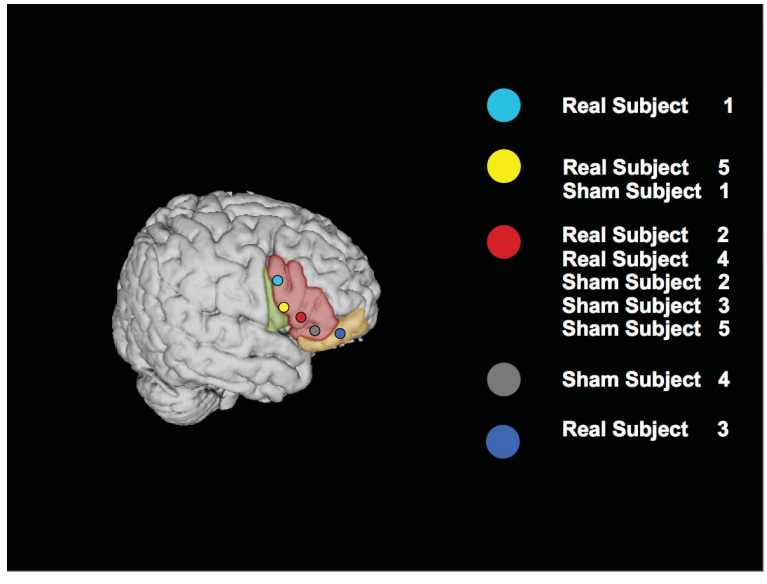

Figure 3. Right hemisphere overlay of optimal real TMS sites for the 10 participants in the study mapped onto the Colin27 MNI template. Participants are labelled as Real or Sham participants 1–5 (based on which type of treatment they received first, although the sites shown all correspond to their real TMS sites), and correspond with participant labels in Table 1. Shading indicates gyral anatomy: Green = pars opercularis, Red = pars triangularis, Yellow = pars orbitalis. To view this figure in colour, please see the online issue of the journal.

2-month sTMS follow-up as well. Speech samples were recorded digitally and coded offline by an experimenter (CN). The order of sessions was randomised during coding and the coder was blinded with respect to participant condition and session order.

Measures of fluency

A variety of elements were quantified in each speech sample using QPA (Saffran et al., 1989). We categorised these variables based on four aspects of speech fluency: discourse productivity, sentence productivity, grammatical accuracy, and lexical selection (Gordon, 2006).

Discourse productivity. This category described the production of words related to the picture stimulus. Narrative words (NW) were defined as the total words minus stereotyped utterances, task-related comments, or comments cued by the narrator. The number of narrative words that were verbs and nouns was recorded, as was the number of unique verbs and nouns. Closed-class words (CCW) were defined as the number of narrative words that were determiners, pronouns, conjunctions, and prepositions; other words were counted as open-class words (OCW). The duration and rate (measured in words per minute) of participants' speech samples were also recorded.

Sentence productivity. This category quantified the length and complexity of sentences. Mean sentence length was defined as the average of the number of words per

utterance containing a noun and a main verb. Median utterance length referred to the number of narrative words per utterance. The sentence elaboration index is a composite score of the number of narrative words per phrase for both noun and verb phrases. The embedding index is the proportion of sentences that contain an embedded clause.

Grammatical accuracy. This category included the proportion of sentences that were well-formed, in that they contain a subject, predicate, and direct object (where necessary). The auxiliary score was defined as an index of the morphological complexity of the main verb of the sentence. The inflexion index is a measure of verbs that have been changed from their base form.

Lexical selection. This category measured the usage words relative to other words in an utterance. The proportion of CCWs reflected the number of CCWs relative to the total number of narrative words. Similarly, the proportion of pronouns and the proportion of verbs relative to total narrative words were also measured.

In addition to QPA, speech samples were also scored with respect to Correct Information Units (CIUs), which were defined as the number of words that were intelligible, accurate, informative, and relevant to the eliciting stimulus (see Nicholas & Brookshire, 1993).

Analysis

We pursued a within-participants comparison contrasting performance 2 months after real rTMS to baseline performance in all participants ($N = 10$), using raw performance scores as dependent variables. Because we had strong a priori predictions about the direction of change likely to be induced by rTMS based on prior evidence (e.g., Barwood et al., 2011; Hamilton et al., 2010; Naeser et al., 2005), one-tailed *t*-tests were employed. We also used within-participants comparisons to contrast 2-month follow-up performance to baseline performance after sTMS in the subset of participants receiving sham stimulation ($N = 5$), using raw performance scores as dependent variables. To confirm that significant rTMS vs baseline effects did not result from practice effects or bias due to unblinding in patients crossed over from the sham arm to the real rTMS arm, we performed a between-participants comparison contrasting the proportion change from baseline to 2-month follow-up on each study measure in patients who received sTMS ($N = 5$) to those who received rTMS initially ($N = 5$), using independent samples one-tailed *t*-tests. For all independent samples *t*-tests (using PASW 18), we used a Levene's test for equality of variances to test for homogeneity of variance. When assumptions of homogeneity of variance were not met, we adjusted the degrees of freedom using the Welch-Satterthwaite method. We did not make any explicit corrections for multiple comparisons as many of the variables were complementary, consisting of subdivisions of other variables (e.g., total nouns and verbs as part of narrative words). Furthermore, it has been suggested that, in exploratory studies, one should not correct for multiple comparisons but instead present the *p*-values for all tests for interpretation (see Rothman, 1990). Note that, given the number of comparisons we are presenting in the paper (21), we would expect about one comparison to be significant if the data were generated at chance.

RESULTS

Comparison of real rTMS to baseline

All participants tolerated stimulation without complaint of physical discomfort or other adverse effects. First we used *t*-tests to observe if there were any differences in baseline performance between participants who received real rTMS initially versus those who received real rTMS after sTMS. For all 21 dependent variables we did not find any significant differences between the two groups in baseline performance (average *p*-value, .521, range, .131–.979), performance at 2-month follow-up (average *p*-value, .494; range, .059–.984), or proportional change from baseline (average *p*-value, .468; range, .113–.879). Therefore results from these two groups were collapsed for the first analysis. The participants demonstrated a significant increase in discourse productivity (see Figure 4), as shown by the significant increase in the number of narrative words 2 months post-treatment compared to baseline, $t(9) = -2.07$, $p = .035$. Within narrative words, we found that participants demonstrated a significant increase in production of open-class words, $t(9) = -2.02$, $p = .037$, closed-class words, $t(9) = -1.95$, $p = .042$, total number of verbs, $t(9) = -2.28$, $p = .024$, unique nouns, $t(9) = -2.02$, $p = .037$, and marginal effects for total number of nouns, $t(9) = -1.82$, $p = .051$, and unique words, $t(9) = -1.63$, $p = .068$. We found no effect for unique verbs, $t(9) = -0.015$, $p = .494$. Consistent with the notion that participants were generating more words relevant to the picture stimulus, there was a trend towards an increase in the number of CIUs generated, $t(9) = -1.60$, $p = .072$. These increases in narrative productivity were not due to participants speaking for longer

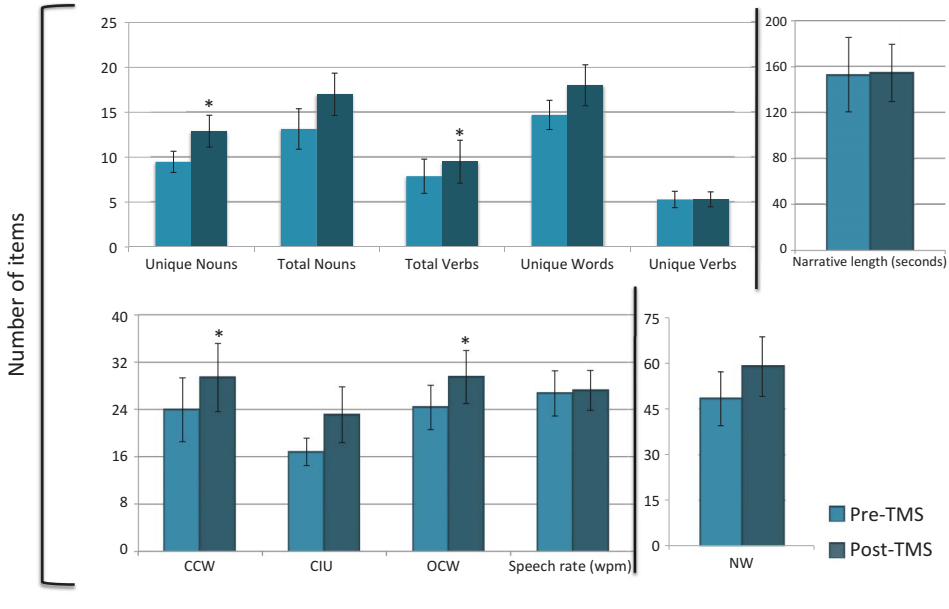

Figure 4. Performance on measures of discourse productivity before and 2 months after receiving real rTMS ($N = 10$). Vertical lines represent standard error. Significant improvement ($p = <.05$) is indicated by "*". NW = Narrative Words; CCW = Closed-class Words; OCW = Open-class Words; CIU = Correct Information Units.

periods of time, as there was only a 1.6-second difference in mean passage length, $t(9) = -0.13$, $p = .449$, between baseline and 2-month follow-up. Nor were participants simply speaking more rapidly, since there was no significant change in speech rate $t(8) = -2.70$, $p = .397$. However, participants showed a marginally significant increase in the total number of utterances before versus after treatment, $t(9) = -1.68$, $p = .064$, and also trend toward significance, $t(9) = -1.72$, $p = .059$, in the percentage of narrative words over total words uttered 2 months after treatment (73.6%) versus at baseline (69.5%).

There was no significant improvement among participants receiving sTMS for any measure of discourse productivity. In contrast to findings within the category of discourse productivity, no significant changes in performance were seen along any variables in the other three fluency categories—sentence productivity, grammatical accuracy, and lexical selection—for either the real rTMS or sTMS conditions (see Figure 5 a–c; see also Supplementary Table 1).

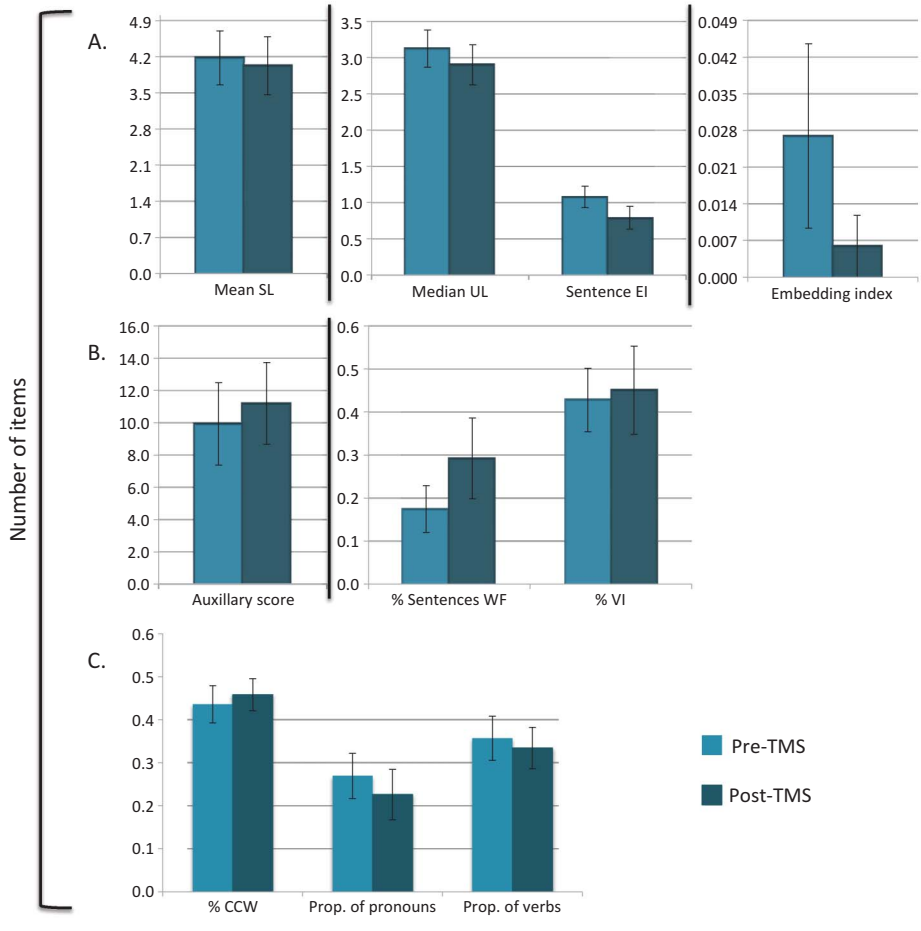

Figure 5. Performance on measures of **(A)** sentence productivity, **(B)** grammatical accuracy, and **(C)** lexical selection ($N = 10$) before and 2 months after real TMS stimulation ($N = 10$). Vertical lines represent the standard error. CCW = Closed-class Words; SL = Sentence Length; UL = Utterance Length; EI = Elaboration Index; WF = Well-formed; VI = Verbs Inflected; Prop. = Proportion.

Comparison of real rTMS to sTMS

Unfortunately the statistical power to make comparisons between participants who had initially received rTMS compared to those who had initially received sTMS was limited due to the small sample size. There was a significantly greater increase from baseline in the use of closed-class words for participants receiving rTMS compared to participants receiving sTMS, $t(7.4) = -2.10$, $p = .036$. There were also trends towards greater change from baseline in participants receiving rTMS compared to participants receiving sTMS for other measures of discourse productivity, including narrative words, $t(6.77) = -1.87$, $p = .053$, unique words, $t(7.73) = -1.65$, $p = .070$, unique nouns, $t(6.32) = -1.48$, $p = .094$, unique verbs, $t(7.47) = -1.78$, $p = .058$, open-class words, $t(7.54) = -1.59$, $p = .076$, and CIUs, $t(5.3) = 1.7$, $p = .072$. No significant differences or trends were found for any measures of sentence productivity, grammatical accuracy, or lexical selection (all p-values $> .1$). Finally there was a very consistent direction of numerical change across all measures of narrative word generation, with participants receiving rTMS showing a greater improvement from baseline than participants receiving sTMS. No consistent pattern of performance emerged across measures of sentence productivity, grammatical accuracy, or lexical selection (see Supplementary Table 2).

DISCUSSION

Our data indicate that individuals with chronic nonfluent aphasia who undergo rTMS of the right inferior frontal gyrus experience improvement in fluency 2 months after treatment. This improvement in fluency is driven specifically by changes in discourse productivity, as indicated by significant increases in a variety of narrative word types following stimulation. Moreover, the increase in narrative comments exhibited by participants after receiving real rTMS is not the result of an increase in the speaking speed or duration, but instead reflects a shift in the distribution of utterances away from irrelevant non-narrative statements towards comments that are relevant to the presented picture stimulus. By contrast, our data indicate that participants with chronic nonfluent aphasia receiving rTMS of the RIFG do not experience a significant benefit with respect to other aspects of fluency, including sentence complexity, grammatical accuracy, or lexical selection.

A few prior investigations have suggested that chronic aphasic individuals receiving right hemisphere stimulation experience improvements in fluency. However, one significant limitation of most of these prior studies is the small number of measures used to quantify this aspect of language production. Naeser and colleagues (2005) reported that two out of four participants receiving rTMS of the IFG experienced an increase in phrase length when describing the Cookie Theft Picture. Martin and colleagues (2009) reported similar results in a single participant. Extending these results to a larger cohort of participants, Barwood and colleagues (2011) reported that rTMS treatment improved picture description in six participants receiving real rTMS treatment compared to six other participants receiving sTMS. However, they only reported two fluency measures: picture description complexity and longest words per phrase. We reported a single case of a chronic aphasic individual who experienced significant and persistent improvement in spontaneous elicited speech on the Cookie Theft Picture Description task and on the Western Aphasia Battery Spontaneous speech subscale (Kertesz, 1982) after receiving 1Hz rTMS of the right IFG (Hamilton et al.,

2010). Unlike prior studies we examined a variety of speech production indices, and found that the participant experienced significant increases in narrative words, different nouns, mean sentence length, and closed-class words per sentence. We also recently reported a single case in which a chronically aphasic participant experienced an increase in the number of unique words employed and a marginal increase in the CIUs during a picture description 2 months after receiving real rTMS (Turkeltaub, Coslett, et al., 2011). The current study builds on our prior findings, confirming in one of the largest reported cohorts of chronic aphasic participants receiving rTMS to date that inhibitory rTMS of the RIFG improves fluency, and clarifying that this effect is related specifically to improved discourse productivity.

The mechanisms by which rTMS of the RIFG improves discourse productivity in individuals with chronic nonfluent aphasia are unclear. However, the performance patterns observed in our participants militate against certain explanations. One possible account for the increase in narrative words is that TMS facilitates speech via mechanisms that are only indirectly related to language functions, for example by diminishing frontal lobe mediated behavioural inhibition or by modulating arousal. However, this account would predict that participants would experience an overall increase in speech production, and does not adequately explain why our participants experience a shift in the distribution of their words towards narrative utterances and away from non-narrative utterances. Neither do our results accord with the notion that rTMS is principally affecting motor aspects of speech production, since this also would not explain a shift towards narrative utterances.

While our findings help to identify which aspects of language production are affected by RIFG rTMS, they do not resolve ongoing debate regarding the neural mechanisms mediating stimulation effects in persons with chronic aphasia. Much of this debate centres on the role of right hemisphere structures in aphasia recovery. One account is that the right hemisphere is deleterious to language recovery, possibly due to the presence of inhibitory interhemispheric connections from the right to the left hemisphere that diminish the recovery of perilesional left hemisphere language areas. A competing account argues that the role of the right hemisphere in aphasia recovery is largely compensatory, and that inhibitory rTMS of specific right hemisphere sites modulates the efficiency of compensatory right hemisphere networks (Hamilton et al., 2011). Based on data from prior imaging studies (Turkeltaub, Messing, Norise, & Hamilton, 2011) and from one specific participant with chronic aphasia who received rTMS and then experienced a second stroke affecting her right hemisphere (Turkeltaub, Coslett, et al., 2011), we have argued that the role of some right hemisphere regions appears to be compensatory while that of other regions appears to interfere with language processing (Hamilton et al., 2011).

One plausible explanation for the current results is that rTMS of the RIFG selectively improves lexical-semantic access. Lexical-semantic access is often profoundly delayed in participants with non-fluent aphasia (Edwards, 1995). Participants who have received inhibitory stimulation may be better able to retrieve the appropriate representations of words and word meanings, and are thus better able to generate more narrative utterances that are relevant to the picture stimulus presented to them. Supporting this notion, all of the study measures in which our participants showed improvement involved accessing words in various categories, with no improvement in measures of grammatical complexity or sentence construction. Improvement in lexical-semantic processing is also consistent with the already established finding that stimulation of this region improves naming, a process that also relies in large part on

the retrieval of accurate lexical-semantic representations (Martin et al., 2004; Naeser et al., 2005, 2010; Winhuisen et al., 2005). The fact that the optimal site during TMS site-finding in our study is the RPTr in 9 out of 10 participants further suggests that inhibition of this specific site has a facilitative effect on lexical-semantic selection (see also Naeser et al., 2011). Furthermore, it has also been shown that rTMS presented to the RPTr in patients with chronic nonfluent aphasia induces changes in the N400 signal (Barwood et al., 2011), an ERP marker that has been associated with lexical-semantic aspects of language processing (Brown & Hagoort, 1993; Halgren et al., 2002; Kutas & Federmeier, 2000; Simos, Basile, & Papanicolaou, 1997).

The notion that TMS of the right PTr might selectively affect lexical-semantic processing is consistent with converging evidence suggesting that individuals with aphasia engage right hemisphere structures during language processing and that these right hemisphere areas are functionally specific. A recent meta-analysis of neuroimaging studies in aphasia indicates that many right hemisphere perisylvian regions that are activated during language tasks in aphasic individuals are homotopic and functionally homologous with left hemisphere areas that normally subserve language in normal persons (Turkeltaub, Messing, et al., 2011). By contrast the right PTr, while homotopic in location with an area of activation in controls, was not homologous with respect to functional activity. Turkeltaub and colleagues suggested that activation observed in the right PTr in aphasic individuals may be dysfunctional, a view further supported by studies that have associated increased right IFG activation with overt naming errors in aphasic participants (Postman-Caucheteux et al., 2010). A number of studies have demonstrated that, in healthy participants, more ventral-anterior regions of the left IFG (including PTr) are preferentially involved in lexical-semantic processing, while posterior-dorsal areas (including the pars opercularis; POp) are preferentially involved in phonology (Bookheimer, 2002; Gough, Nobre, & Devlin, 2005; Hagoort, 2005; Poldrack et al., 1999). Moreover, Hartwigsen and colleagues (2010) found that in healthy individuals disruption of the right POp with TMS resulted in worsened performance on a phonological selection task, while disruption of the right PTr had no effect on a matched semantic task. This finding suggests that, although it is homotopic with a LIFG region that mediates lexical-semantic processing in normal persons, the right PTr is poorly suited to support recovery of lexical-semantic processing after LIFG injury. This is consistent with functional imaging data in aphasia demonstrating that left hemisphere activation was associated with phonemic naming errors, but right hemisphere activity was associated with semantic naming errors (Fridriksson, Baker, & Moser, 2009). By this account, inhibition of overactivity in the right PTr might result in suppression of an inefficient node in the remodelled language network that otherwise contributes deleteriously to lexical-semantic processing.

The current study has limitations. Even though this is one of the largest studies to report on the effects of rTMS on language ability in persons with chronic nonfluent aphasia the study is still underpowered, and additional investigations in larger cohorts of participants are needed to establish the impact of rTMS on measures of fluency more definitively. Also the number of speech samples gathered from each participant was relatively low compared to the volume of data collected in the original studies validating the QPA (Berndt, Wayland, Rochon, Saffran, & Schwarz, 2000) and the use of CIUs (Nicholas & Brookshire, 1993). Baseline testing was not repeated for participants who initially received sham stimulation prior to receiving real rTMS. While it is therefore possible that introduction of sham rTMS and a 2-month time interval could have resulted in a different baseline level of performance for these individuals,

the absence of change on any study measure between baseline and 2-month follow-up in participants who had received sTMS argues against this claim. Finally, owing to the difference in sensory experience between real and sham stimulation, we cannot exclude the possibility that some participants were not fully blinded to their condition when receiving sTMS. It should be noted, however, that no participant had received TMS prior to the study and therefore would not have had expectations regarding the sensory experiences associated with TMS. Despite these caveats, the current data suggest that in addition to improving naming ability rTMS may be a promising technique for remediating dysfluency, one of the most debilitating deficits for many patients with chronic aphasia.

REFERENCES

Barwood, C. H., Murdoch, B. E., Whelan, B. M., Lloyd, D., Riek, S., O'Sullivan, J. D., . . . Wong, A. (2011). Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. *European Journal of Neurology*, *18*, 935–943.

Berndt, R. S., Wayland, S., Rochon, E., Saffran, E., & Schwartz, M. (2000). *Quantitative production analysis: A training manual for the analysis of aphasic sentence production*. Philadelphia, PA: Psychology Press.

Bookheimer, S. (2002). Functional MRI of language: New approaches to understanding the cortical organization of semantic processing. *Annual Review of Neuroscience*, *25*, 151–88.

Brown, C., & Hargoort, P. (1993). The processing nature of the N400: Evidence from masked priming. *Journal of Cognitive Neuroscience*, *5*, 34–44.

Edwards, S. (1995). Profiling fluent aphasic spontaneous speech: A comparison of two methodologies. *European Journal of Disorders of Communication*, *30*, 333–345.

Fridriksson, J., Baker, J. M., & Moser, D. (2009). Cortical mapping of naming errors in aphasia. *Human Brain Mapping*, *30*, 2487–2498.

Gleason, J. B., Goodglass, H., Green, E., Ackerman, N., & Hyde, M. R. (1975). The retrieval of syntax in Broca's aphasia. *Brain & Language*, *2*, 451–471.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). *Boston Diagnostic Aphasia Examination (BDAE)*. Philadelphia, PA: Lippincott, Williams & Wilkins.

Gordon, J. K. (2006). A quantitative production analysis of picture description. *Aphasiology*, *20*, 188–204.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience*, *25*, 8010–8016.

Hagoort, P. (2005). On Broca, brain, and binding: A new framework. *Trends in Cognitive Science*, *9*, 416–423.

Halgren, E., Dhond, R. P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J. D., & Dale, A. M. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage*, *17*, 1101–1116.

Hamilton, R. H., Chrysikou, E. G., & Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain & Language*, *118*, 40–50.

Hamilton, R. H., Sanders, L., Benson, J., Faseyitan, O., Norise, C., Naeser, M., . . . Coslett, H. B. (2010). Stimulating conversation: Enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. *Brain & Language*, *113*, 45–50.

Hartwigsen, G., Price, C. J., Baumgaertner, A., Geiss, G., Koehnke, M., Ulmer, S., & Siebner, H. R. (2010). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: Evidence from dual-site TMS. *Neuropsychologia*, *48*, 3155–3163.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston Naming Test (BNT)*. Austin, TX: Lippincott Williams & Wilkins.

Kertesz, A. (1982). *Western aphasia battery*. New York, NY: Grune & Stratton.

Kolk, H., & Heeschen, C. (1990). Adaptation symptoms and impairment symptoms in Broca's aphasia. *Aphasiology*, *4*, 221–231.

Kutas, M., & Federmeier, K. D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Science*, *4*, 463–470.

Martin, P. I., Naeser, M. A., Ho, M., Doron, K. W., Kurland, J., Kaplan, J., . . . Pascual-Leone, A. (2009). Overt naming fMRI pre- and post-TMS: Two nonfluent aphasia patients, with and without improved naming post-TMS. *Brain & Language*, *111*, 20–35.

Martin, P. I., Naeser, M. A., Theoret, H., Tormos, J. M., Nicholas, M., Kurland, J., . . . Pascual-Leone, A. (2004). Transcranial magnetic stimulation as a complementary treatment for aphasia. *Seminars in Speech and Language*, *25*, 181–191.

Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Kobayashi, M., . . . Pascual-Leone, A. (2005). Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. *Brain & Language*, *93*, 95–105.

Naeser, M. A., Martin, P. I., Theoret, H., Kobayashi, M., Fregni, F., Nicholas, M., . . . Pascual-Leone, A. (2011). TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. *Brain & Language*, *119*, 206–213.

Naeser, M. A., Martin, P. I., Treglia, E., Ho, M., Kaplan, E., Bashir, S., . . . Pascual-Leone, A. (2010). Research with rTMS in the treatment of aphasia. *Restorative Neurology and Neuroscience*, *28*, 511–529.

Nicholas, L. E., & Brookshire, R. H. (1993). A system for quantifying the informativeness and efficiency of the connected speech of adults with aphasia. *Journal of Speech and Hearing Research*, *36*, 338–350.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage*, *10*, 15–35.

Postman-Caucheteux, W. A., Birn, R. M., Pursley, R. H., Butman, J. A., Solomon, J. M., Picchioni, D., . . . Braun, A. R. (2010). Single-trial fMRI shows contralesional activity linked to overt naming errors in chronic aphasic patients. *Journal of Cognitive Neuroscience*, *22*, 1299–1318.

Rochon, E., Saffran, E. M., Berndt, R. S., & Schwartz, M. F. (2000). Quantitative analysis of aphasic sentence production: Further development and new data. *Brain & Language*, *72*, 193–218.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., . . . Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN Committee. *Electroencephalography and Clinical Neurophysiology*, *91*, 79–92.

Rothman, K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology*, *1*, 43–46.

Saffran, E. M., Berndt, R. S., & Schwartz, M. F. (1989). The quantitative analysis of agrammatic production: Procedure and data. *Brain & Language*, *37*, 440–479.

Simos, P. G., Basile, L. F., & Papanicolaou, A. C. (1997). Source localization of the N400 response in a sentence-reading paradigm using evoked magnetic fields and magnetic resonance imaging. *Brain Research*, *762*, 29–39.

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning*, *6*, 174–215.

Turkeltaub, P. E., Coslett, H. B., Thomas, A. L., Faseyitan, O., Benson, J., Norise, C., & Hamilton, R. H. (2011). The right hemisphere is not unitary in its role in aphasia recovery. *Cortex*. Advance online publication.

Turkeltaub, P. E., Messing, S., Norise, C., & Hamilton, R. H. (2011). Are networks for residual language function and recovery consistent across aphasic patients? *Neurology*, *76*, 1726–1734.

Weiduschat, N., Thiel, A., Rubi-Fessen, I., Hartmann, A., Kessler, J., Merl, P., . . . Heiss, W. D. (2011). Effects of repetitive transcranial magnetic stimulation in aphasic stroke: A randomised controlled pilot study. *Stroke*, *42*, 409–415.

Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2005). Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: A combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke*, *36*, 1759–1763.