Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain and Language 93 (2005) 95–105
Brain and Language
www.elsevier.com/locate/b&l

Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study

Margaret A. Naeser[a,*], Paula I. Martin[a], Marjorie Nicholas[a], Errol H. Baker[a], Heidi Seekins[a], Masahito Kobayashi[b], Hugo Theoret[b,c], Felipe Fregni[b], Jose Maria-Tormos[d], Jacquie Kurland[a], Karl W. Doron[a], Alvaro Pascual-Leone[b,d]

[a] *Department of Neurology, Harold Goodglass Boston University Aphasia Research Center, Boston University School of Medicine and the Veterans Affairs Boston Healthcare System, USA*
[b] *Center for Non invasive Brain Stimulation, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, USA*
[c] *Département de Psychologie and Hôpital Ste-Justine, Université de Montréal, Canada*
[d] *Institut Guttmann de Neurorehabilitación, Instituto Universitario, Universidad Autónoma de Barcelona, Spain*

Accepted 20 August 2004
Available online 7 October 2004

Abstract

Functional imaging studies with nonfluent aphasia patients have observed "over-activation" in right (R) language homologues. This may represent a maladaptive strategy; suppression may result in language improvement. We applied slow, 1 Hz repetitive transcranial magnetic stimulation (rTMS) to an anterior portion of R Broca's homologue daily, for 10 days in four aphasia patients who were 5–11 years poststroke. Significant improvement was observed in picture naming at 2 months post-rTMS, with lasting benefit at 8 months in three patients. This preliminary, open trial suggests that rTMS may provide a novel treatment approach for aphasia by possibly modulating the distributed, bi-hemispheric language network.
Published by Elsevier Inc.

Keywords: Aphasia; TMS; Naming; Stroke rehabilitation

1. Introduction

Brain re-organization for language recovery after left hemisphere (LH) stroke in patients with aphasia remains unknown. Evidence suggesting a right hemisphere (RH) role dates back to the late 1800s (Barlow, 1877; Gowers, 1886). Nearly a century later, this was further supported by amobarbital studies with aphasia patients where injection into the R carotid produced speech arrest in most patients, whereas injection into the left side produced almost no alteration on aphasic speech (Czopf, 1972; Kinsbourne, 1971). More recently, Basso, Gardelli, Grassi, and Mariotti (1989) reported that patients who had partially recovered from aphasia after LH lesion showed worsening of language functions after subsequent RH lesion.

Some studies have suggested that both RH and LH participation is beneficial in aphasia recovery. In functional imaging studies with Wernicke's aphasia patients, increased activation in the right posterior superior temporal gyrus region (and some remaining LH language areas) has been associated with improvement (Musso et al., 1999; Weiller et al., 1995). Areas of RH activation during language tasks may be limited to homologous areas that were damaged in the LH (Calvert et al., 2000; Lazar et al., 2000; Thulborn, Carpenter, & Just, 1999). Kim, Ko, Parrish, and Kim (2002) have suggested that right frontal reorganization may depend on intact left basal ganglia. Other studies have suggested that

* Corresponding author. Present address: V.A. Boston Healthcare System (12A), 150 So. Huntington Avenue, Boston, MA 02130, USA. Fax: +1 617 739 8926.
E-mail address: mnaeser@bu.edu (M.A. Naeser).

0093-934X/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.bandl.2004.08.004

RH participation is present when there is greater damage to LH language areas (Cao, Vikingstad, George, Johnson, & Welch, 1999; Demeurisse & Capon, 1987; Heiss et al., 1997; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Karbe, Thiel, & Weber-Luxenburger, 1998, 1998a). The latter authors have observed that patients with better overall recovery had higher activation in the L superior temporal gyrus area (and the L SMA). Warburton, Price, and Swinburn (1999) and Miura, Nakamura, and Miura (1999) have observed better recovery to be associated with LH activation. Several functional imaging studies have observed new LH activation to be associated with language improvement following speech therapy (Cornelissen et al., 2003; Leger, Demonet, & Ruff, 2002; Musso et al., 1999; Small, Flores, & Noll, 1998).

Functional imaging studies where *only nonfluent* aphasia patients were examined have observed unusually high activation levels in R perisylvian language homologues during various language tasks (Belin et al., 1996; Naeser et al., 2004; Rosen et al., 2000). Belin et al. (1996) reported significant increases in the R sensorimotor mouth region, R prefrontal, R Wernicke's, and R anterior superior temporal gyrus during overt, nonfluent bisyllabic single word repetition (versus hearing words) in seven chronic, nonfluent aphasia patients. A significant decrease in L Broca's area was also observed. Rosen et al. (2000) reported a stronger-than-normal response in the R inferior frontal gyrus region during overt (PET) and covert (fMRI) word stem completion tasks with 6 stroke patients who had L inferior frontal gyrus lesions, who were studied at least 6 months poststroke onset (MPO). Naeser et al. (2004) observed a significant increase in R sensorimotor mouth and R supplementary motor area (SMA) during overt propositional speech in four nonfluent aphasia patients, who were studied 4–9 years poststroke.

Whether R hemisphere activation observed during functional imaging in nonfluent aphasia patients is beneficial or maladaptive remains to be clarified. Belin et al. (1996) have suggested that increased, abnormal activation patterns in the lesioned brain may not necessarily be related to recovery. The increased activation may be a marker of failed or faulty recovery attempts in the sense of maladaptive plasticity or the breakdown of normal inter-hemispheric control within a distributed neural network for a language task. High RH activation is not necessarily correlated with improved language performance (Naeser et al., 2004; Perani et al., 2003; Rosen et al., 2000). Rosen et al. (2000) concluded that "...the anomalous R frontal response after L frontal damage may reflect the loss of active inhibition or competitive interaction from the homologous L frontal area, or an inefficient 'dead-end' strategy."

1.1. Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) of appropriate frequency, intensity and duration can lead to transient increases or decreases in excitability of the targeted cortex that last beyond the duration of the rTMS train itself (Pascual-Leone et al., 1998). Slow (1 Hz) rTMS has been shown to decrease cortical excitability in humans (Chen et al., 1997; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). Slow, 1 Hz rTMS applied to the motor cortex can give rise to a lasting decrease in corticospinal excitability primarily by affecting intracortical facilitation (Romero, Anshel, Sparing, Gangitano, & Pascual-Leone, 2002). Applied to other cortical regions, slow rTMS appears to similarly decrease excitability in the targeted cortical region leading to measurable behavioral effects (Hilgetag, Theoret, & Pascual-Leone, 2001; Kosslyn et al., 1999; Mottaghy, Gangitano, Sparing, Krause, & Pascual-Leone, 2002; Robertson, Tormos, Maeda, & Pascual-Leone, 2001; Theoret, Haque, & Pascual-Leone, 2001). Conversely, fast rTMS (5, 10 or 20 Hz) can induce a transient increase in cortical excitability (Berardelli et al., 1998; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994).

The possibility of modulating cortical excitability with rTMS has generated trials applying rTMS to treat various neuropsychiatric conditions. The hypothesis underlying most studies is that modulation of cortical excitability in cortical areas of dysfunction (as evidenced by functional neuroimaging) may result in clinical benefit (George & Bellmaker, 2000; Pascual-Leone et al., 1998). For example, slow, 1 Hz rTMS has been studied to treat schizophrenia (Klein et al., 1999); depression (Klein et al., 1999a); and epilepsy (Tassinari, Cincotta, Zaccara, & Michelucci, 2003; Tergau, Naumann, Paulus, & Steinhoff, 1999), to name a few. Slow, 1 Hz rTMS appears capable of normalizing abnormally enhanced motor cortical excitability in some patients with dystonia, and has led to symptomatic improvement for hours to days (Siebner et al., 1999). In RH stroke patients who have left-sided neglect, slow, 1 Hz rTMS has been applied to the posterior parietal area in the undamaged LH. A significant reduction in the severity of neglect was observed for 2 weeks, following seven treatments over a 2-week period (900, 1-Hz pulses, 90% of motor threshold) (Brighina et al., 2003). Similar improvement in neglect has been observed in other rTMS studies with these patients (Hilgetag et al., 2001; Oliveri et al., 1999). Repetitive TMS has an effect on language, ranging from facilitation of naming (Mottaghy et al., 1999) to speech arrest (Epstein et al., 1999; Pascual-Leone, Gates, & Dhuna, 1991) depending on rTMS parameters and location of the coil.

1.2. Transcranial magnetic stimulation in aphasia

We have observed that application of slow, 1 Hz rTMS for 10 min to an *anterior* portion of R Broca's homologue in stroke patients with chronic, nonfluent aphasia results acutely in a significant increase in ability to name pictures, and a significant decrease in reaction time (Naeser et al., 2002). In that study, we observed that precise placement of the TMS coil (within 1 or 2 cm) within R Broca's homologue was important, and could produce significantly different effects on naming. That study is reviewed briefly.

Broca's region in the LH is classically defined as the foot of the third frontal convolution (Broca, 1861). In the left inferior frontal gyrus, this region includes the pars triangularis (anterior portion of Broca's area), and the pars opercularis (posterior portion of Broca's area). These two areas are often referred to in cytoarchitectonic studies as Brodmann areas (BA) 45 and 44, respectively, although cytoarchitectonic borders do not consistently coincide with sulcal contours (Amunts et al., 1999). These two areas in the inferior frontal gyrus are anatomically separated by the anterior, vertical (ascending) ramus of the Sylvian fissure. See Devlin, Matthews, and Rushworth (2003) for review.

In our previous rTMS study with six aphasia patients, we studied the effect of slow, 1 Hz rTMS for 10 min (600 pulses at 90% motor threshold) to suppress activity in each of four different cortical areas in the RH perisylvian region (homologous language areas). A figure-8 shaped rTMS coil was used with a 7 cm outside diameter on each wing. The approximate size of cortical area stimulated was 1 cm × 1 cm. Our targeted areas included: (1) an *anterior* portion of R Broca's homologue where the coil was placed over a gyrus immediately rostral to the anterior, (vertical) ascending ramus of the Sylvian fissure (referred to as pars triangularis in our studies); (2) a *posterior* portion of R Broca's homologue where the coil was placed over a caudal gyrus of the pars opercularis, near the junction with the inferior premotor cortex (referred to as pars opercularis in our studies); (3) the posterior, superior temporal gyrus area (right Wernicke's homologue region); and (4) the right motor cortex, mouth area.

A frameless stereotactic system was used with each patient's three-dimensional magnetization prepared rapid gradient echo (3D MPRAGE) MRI scan to guide coil placement onto the targeted cortical area (Brainsight, Rogue Industries, Montreal) during each session. Application of rTMS to the R pars opercularis area significantly decreased the number of pictures named, relative to baseline, and the reaction times were increased. Application of rTMS to the R pars triangularis area, however, was associated with a significant increase in picture naming, and a significant decrease in reaction time. The R pars triangularis was the only area associated with significant improvement in naming, following a 10-min rTMS treatment (Naeser et al., 2002). The improved naming immediately after rTMS application to this area was only temporary, however, lasting less than a half hour.

The purpose of the present open, pilot study was to investigate whether application of slow rTMS to this anterior portion of R Broca's homologue (R pars triangularis) for 20 min a day (1200, 1-Hz pulses), 5 days a week for 2 weeks, is safe; and whether it is associated with significantly improved picture naming in chronic aphasia patients over a longer period of time post-rTMS, up to two months or more. Our underlying hypothesis was that slow, 1 Hz rTMS would induce inhibition at the site of stimulation, and thus reduce the relative hyperactivity of the healthy, unaffected RH, as observed in previous functional imaging studies with chronic, nonfluent aphasia patients reviewed above (Belin et al., 1996; Naeser et al., 2004; Rosen et al., 2000). It was further hypothesized that suppression of R pars triangularis would have a beneficial effect on the more widespread, bi-hemispheric neural network for naming, affecting other LH and RH regions important for naming, primarily temporal and parietal areas (Bookheimer, Zeffiro, Blaxton, Baillard, & Theodore, 1995; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Friston, Frith, Liddle, & Frackowiak, 1991; Gold & Buckner, 2002; Price, Warburton, Moore, Frackowiak, & Friston, 2001).

2. Methods

2.1. Patients

Four right-handed, chronic aphasia patients participated, at 5–11 years post-L middle cerebral artery stroke. Patient 1 (P1) had recovered from nonfluent Broca's aphasia to anomic/conduction aphasia; he had no R hemiparesis. Patients P2 and P3 had mild and moderate nonfluent Broca's aphasia; and P4, severe nonfluent, global aphasia. Patient 2 had R hemiparesis; P3 and P4, R hemiplegia. The patients did not receive any individualized speech therapy during the study.

2.2. Standardized language testing (primary outcome measures)

Within 1–2 weeks before the first rTMS treatment, patients were tested with the first 20 items of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001) and parts of the Boston Diagnostic Aphasia Exam (BDAE) (Goodglass, Kaplan, & Barresi, 2001), and again at 2 months and 8 months post- the 10th rTMS treatment. Table 1. Abbreviated forms of each test were used in order to limit the testing sessions to one hour. The subtests administered on the BDAE were as follows: spontaneous speech (cookie theft picture descrip-

Table 1
Primary outcome measures, Boston Naming Test (BNT) and Boston Diagnostic Aphasia Exam (BDAE, 3rd. ed.) scores for each aphasia patient, pre-rTMS and at 2 months and 8 months post-rTMS

Patient Aphasia type	P1 Recovered Broca anomic/conduction	P2 Mild nonfluent	P3 Moderate nonfluent	P4 Severe nonfluent/global
Age (years), sex	52, M	58, M	53, M	57, F
Years poststroke at entry testing	5	10	11	7
BNT scores				
First 20 items (max = 20)				
Pre	13	11	4	4
Post-2 months	15	14	6	7
Post-8 months	17	17	4	12
BDAE scores				
Longest number of words per phrase length (max = 7)				
Pre	7	3	1	1
Post-2 months	7	5	3	1
Post-8 months	7	4	1	1
Articulatory agility (max = 7)				
Pre	6.5	5	2	3
Post-2 months	6	5	3	3
Post-8 months	6	5	2.5	3
Repetition of single words (max = 10)				
Pre	7	9	2	4
Post-2 months	8	7	3	4
Post-8 months	8	9	3	3
Repetition of sentences (max = 10)				
Pre	2	2	0	0
Post-2 months	1	2	0	0
Post-8 months	2	4	0	0
Comprehension of single words (max = 37)				
Pre	32.5	30	34	26.5
Post-2 months	31.5	32.5	27	27
Post-8 months	29.5	34	33	30
Commands (max = 15)				
Pre	9	12	13	3
Post-2 months	8	15	12	6
Post-8 months	10	13	12	4

tion, where articulatory agility, phrase length, grammatical form, melodic line, paraphasia in running speech, and word finding relative to fluency were rated); auditory comprehension (word comprehension, commands, and complex ideational material); repetition (single words and sentences); naming screening of special categories (letters, numbers, and colors); and naming in categories (colors, actions, animals, and tools/implements). Patients had to be able to name a minimum of 3 pictures on the first 20 items of the BNT, to qualify for entry into the study. These BNT and BDAE data were the primary outcome measures in the study.

2.3. Snodgrass and Vanderwart picture naming (baseline, and immediate pre- and post-rTMS treatment measures)

Five naming lists (100 pictures) were generated from the standardized set of 260 pictures from Snodgrass and Vanderwart (1980). Each list consisted of 20 pictures. Each of these five lists (Lists A–E) was controlled for frequency and visual complexity. All words were only 1–2 syllables in length; most words were monosyllabic (e.g., bow, church, and hand). Each list contained items from a variety of separate semantic categories (animals, food, body parts, and furniture, etc.). No two sequential words within a list belonged to the same semantic category or had the same initial phoneme. An additional list was used to train the subject to the task. All lists were matched for difficulty in pilot testing on normal subjects (overall mean reaction time = 1116.8 ms; $SD = 362.5$); there were no significant differences among the five lists. Five additional internal randomizations were also prepared (List A1–A6 and List B1–B6, etc.), used for later testing.

Each list was administered to the subject using a laptop computer. Each picture was on the screen for 10 s, with a 1 s inter stimulus interval (ISI) between pictures. Each picture was preceded by a fixation dot and a 120 ms duration tone beep. Subjects were asked to name

the picture as soon as possible, after it was shown. The tone beep and the subject's tape-recorded responses were digitized, and SoundEdit software was used to determine the reaction time (RT) for each response. The visual waveform on the monitor was used to measure the RT from onset of the picture to the onset of the correct name, while ignoring intermediate responses. The RT to the correct response was verified by auditory monitoring.

Within 1–2 weeks before the 1st rTMS treatment, an overall Snodgrass and Vanderwart (S&V) Baseline Naming Ability for each patient was obtained. Each list (A–E) was administered only once to establish an overall S&V Baseline Naming for each patient. This overall S&V Baseline Naming for each patient was measured in two ways: (1) total number of pictures named correctly and (2) RT (using SoundEdit software). In order to qualify for entry into the study, a patient had to be able to name an average of at least three pictures per list, across the five lists (i.e., for entry, an overall S&V Baseline Naming of three was required).

One of the Lists A–E (selected from one of the six different randomizations within each list, List A1–A6 and List B1–B6, etc.) was administered immediately before and immediately after the 1st and 10th rTMS treatments. A different list was used for each of these tests. Pilot testing demonstrated that learning and priming effects on response times for the tasks are negligible even with repeated exposure to the items, given the large number of different pictures presented, the lack of feedback on performance, and the long time interval between testing sessions. Thus, the S&V naming data provided information on naming ability and reaction time pre-rTMS, as well as immediately post-rTMS (within 10 min) following the 10th rTMS treatment. These data were acquired immediately following the 10th rTMS treatment, to test whether there was any change in naming ability (and RT), as well as to address whether any negative side effects might be present fol-

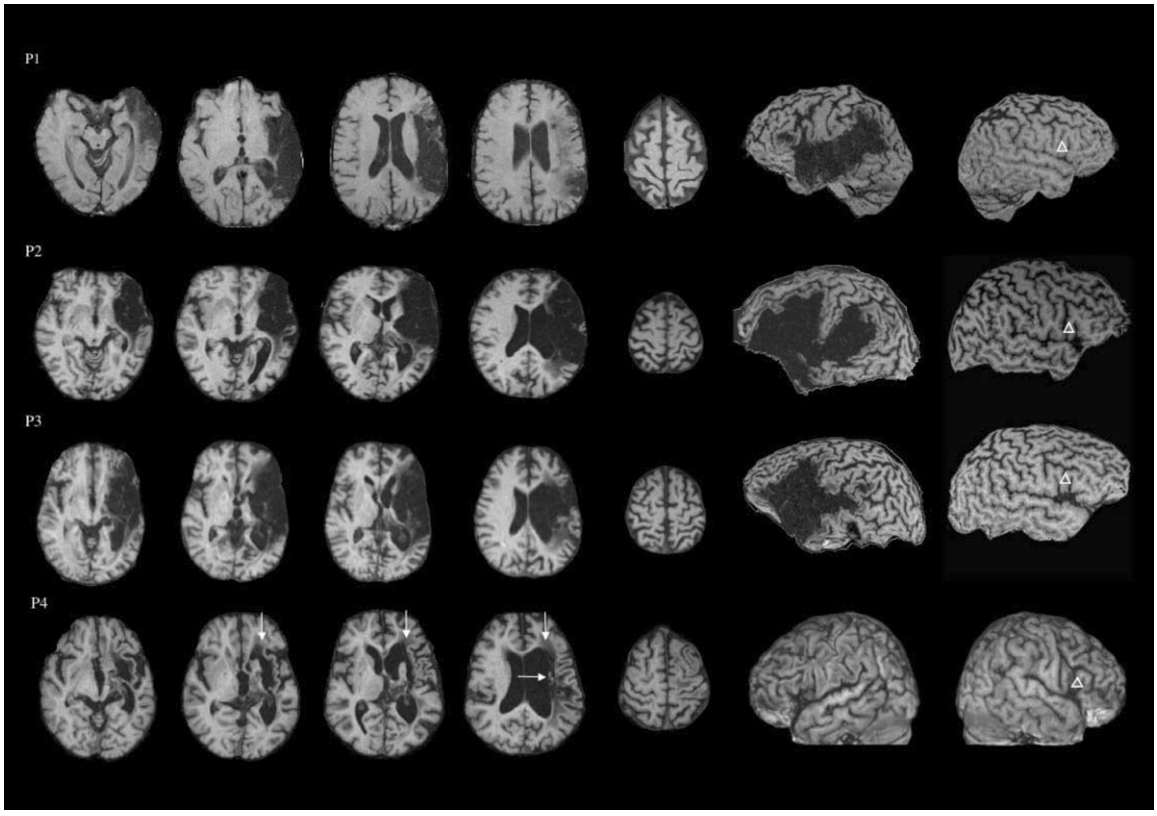

Fig. 1. T1-weighted structural MRI scans for each chronic aphasia patient, 5–11 years poststroke, showing L hemisphere lesion. The L and R lateral views are reconstructed from a 3D MPRAGE MRI scan. The white triangle in R Broca's homologue marks the area of cortex that was suppressed with 1 Hz rTMS during each 20-min treatment session. This area was immediately rostral to the vertical (ascending) ramus of the Sylvian fissure. Patients P1–P3 had some lesion in L Broca's cortical area (pars triangularis and pars opercularis), however, the most severe patient, P4, with subcortical lesion only, did not. She had extensive lesion present in the two white matter areas near ventricle, compatible with severe nonfluent speech: (1) the medial subcallosal fasciculus, deep to Broca's area adjacent to the L frontal horn (vertical arrows); plus (2) the periventricular white matter, located deep to sensorimotor cortex, adjacent to the L body of lateral ventricle (horizontal arrow). See text for pathways in these areas. The mild and moderate nonfluent patients (P2 and P3) also had some lesion in these two, deep white matter areas. The recovered Broca's aphasia patient, P1, had almost no lesion in these two areas.

lowing 10 rTMS treatments in this stroke patient population.

2.4. Patient left hemisphere lesion descriptions

Patients P1–P3 each had L hemisphere lesion that included L cortical Broca's area (pars triangularis and pars opercularis) and white matter deep to it (Fig. 1). The most severe patient, P4, had no lesion in Broca's cortical area but only subcortical lesion, secondary to a basal ganglia bleed. She had extensive lesion in two deep, white matter areas near ventricle, compatible with severe nonfluent speech (Fig. 1, see arrows). These areas included: (1) medial subcallosal fasciculus, located deep to Broca's area, adjacent to L frontal horn (affecting pathways from SMA and cingulate BA 24 to head of caudate); and (2) periventricular white matter, located deep to sensorimotor cortex, adjacent to the L body of lateral ventricle (affecting sensorimotor pathways deep to mouth, inter- and intra-hemispheric pathways including in part, limbic and motor thalamo-cortical pathways) (Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, & Albert, 1989). This study was approved by the Institutional Review Boards at all hospitals where the authors are affiliated and signed informed consent was obtained.

2.5. rTMS treatment procedure

Patients received daily rTMS treatments, 5 days a week for 2 weeks (10 treatments). The targeted anterior part of R Broca's homologue for rTMS was the same as that labeled pars triangularis in our previous study (Naeser et al., 2002). This area was chosen based on prior results from that study. The coil was placed over a gyrus immediately rostral to the anterior, (vertical) ascending ramus of the Sylvian fissure. This area is marked on the right lateral composite image for each patient, as shown in Fig. 1. This area was identified on each patient's 3D MPRAGE MRI scan. On each day of treatment, rTMS was applied at 1 Hz frequency for 20 min (1200 pulses) at 90% of motor threshold (left, first dorsal interosseus muscle), using a Super-Rapid High Frequency MagStim Magnetic Stimulator and a figure 8-shaped coil (MagStim, NY). Each wing of the commercially available coil measured 7 cm in diameter. Mathematical models suggest that when rTMS is applied tangentially to the scalp at perithreshold intensity, this coil affects a volume of approximately 1 cc of cortex (Roth, Saypol, Hallett, & Cohen, 1991). A frameless stereotaxic system (Brainsight, Rogue Industries, Montreal) guided the position of the TMS coil on the patient's scalp. On-line monitoring allowed documentation of accurate targeting of the specified brain area throughout the rTMS session, and from day-to-day, see Fig. 2. Coil orientation was also monitored with Brainsight and it was held constant across sessions and patients, at approximately 45°.

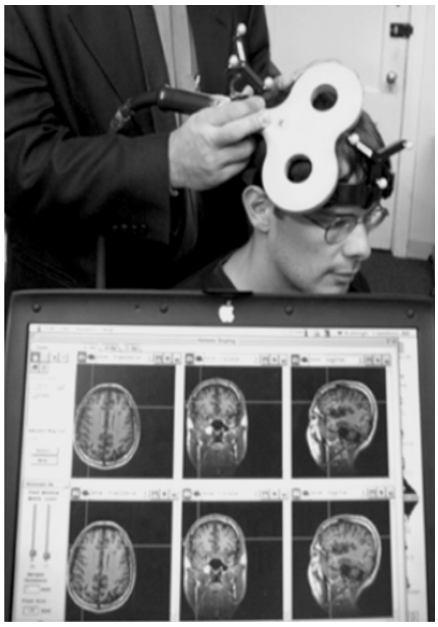

Fig. 2. Illustration showing the TMS equipment and treatment procedure. An infrared camera is used to detect the position of the TMS coil. The 3D MPRAGE MRI scan of the participant is shown on a laptop computer used to guide positioning of the TMS coil directly over the targeted cortical region of interest (Brainsight, Rogue Industries, Montreal, Que.). The figure 8-shaped TMS coil is placed on the participant's scalp to affect brain cortex (approximately 1 cm × 1 cm) directly beneath the center of the coil.

Our rTMS parameters of 1 Hz, 1200 pulses (20 min) at 90% of motor threshold for each of 10 treatments over a 2-week period, are similar parameters to those used in various studies where multiple rTMS treatments were given over time, to help treat depression (Kauffman, Cheema, & Miller, 2004; Klein et al., 1999; Padberg et al., 1999). No negative side effects have been reported with these parameters.

3. Results

3.1. Snodgrass and Vanderwart picture naming (baseline, and immediate pre- and post-rTMS treatment measures)

On a 20-item Snodgrass and Vanderwart list administered immediately following the 10th rTMS treatment, the patients named significantly more pictures than at pre-rTMS/overall S&V Baseline Naming (pre-rTMS mean = 8.1, $SD = 4.2$; post-rTMS mean = 11.5, $SD = 4.7$; and $t = 9.054$, $p = .0028$, two-tailed). The patients also significantly reduced their reaction time to name these pictures (pre-rTMS mean = 3630.5 ms, $SD = 267.1$; post-rTMS mean = 2856.5 ms, $SD = 305.6$; and $t = 3.48$, $p = .04$, two-tailed). These effects were consistent in all patients; each showed the same behavioral

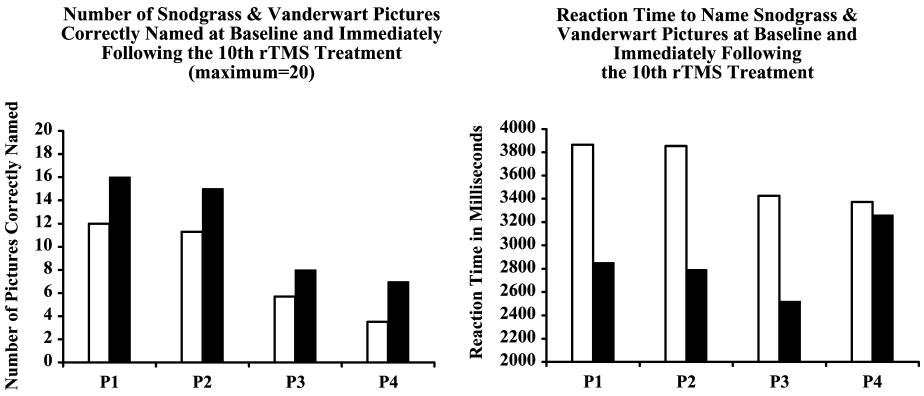

Fig. 3. Graphs showing an increase in the number of pictures named correctly (and a decrease in reaction time) on a randomized list of 20 Snodgrass and Vanderwart pictures shown immediately following the 10th rTMS treatment (black bars), compared to the pre-rTMS/overall S&V Baseline Naming (white bars), for each patient. Each patient showed the same pattern of improvement post-rTMS, despite differences in severity of performance at pre-rTMS/Baseline—i.e., an increase in the number of pictures correctly named ($p = .0028$, two-tailed), and a decrease in reaction time ($p = .04$, two-tailed).

changes despite initial differences in overall S&V Baseline Naming (Fig. 3).

3.2. Standardized language testing (primary outcome measures)

A series of univariate one-way repeated measures analyses of variances were conducted for the various language assessments with time of testing (pre-rTMS; post-2 weeks; 2 months; and 8 months) as the repeated measure. We found a significant main effect of testing time on the first 20 items on the BNT ($f = 5.69$; $df = 3,9$; and $p = .018$) and the BDAE subtests Animal Naming ($f = 4.67$; $df = 3,9$; and $p = .03$) and Tools/Implements Naming ($f = 7.39$; $df = 3,9$; and $p = .008$). Subsequent to the ANOVA, comparisons of individual means were carried out using the Newman–Keuls correction procedure.

Table 2 shows significant improvement in naming on standardized tests (relative to pre-rTMS testing) at specified testing times post-rTMS. At 2 weeks, there was significant improvement on the BDAE subtest, Animal Naming ($p = .02$). At 2 months, there was significant improvement on three naming tests: (1) BNT (first 20 items) ($p = .003$); (2) BDAE subtest, Animal Naming ($p = .02$); and (3) BDAE subtest, Tools/Implements ($p = .04$). At 8 months, all three naming scores continued to improve relative to pre-rTMS, but only Tools/Implements was significant ($p = .003$). BNT and Animal Naming failed to reach significance because of P3 (Fig. 4). There were no other significant changes.

Improvement was also observed in number of words per longest phrase length in elicited, propositional speech for two of the three nonfluent patients when tested with the BDAE at 2 months post-rTMS. Table 1 shows that P2 (mild nonfluent speech) increased from a three-word phrase length, to a five-word phrase length when describing the BDAE cookie theft picture; and P3 (moderate nonfluent) increased from a one-word phrase length, to a three-word phrase length. This increase was not sustained, however, at 8 months post-rTMS.

Table 2
Significance levels for changes in naming scores on three standardized language tests at pre-rTMS, versus 2 weeks, 2 months, and 8 months post-rTMS for the four chronic aphasia patients

	Pre-rTMS	Two weeks post-rTMS	Two months post-rTMS	Eight months post-rTMS
Boston Naming Test				
First 20 items				
Mean	8	8.5	10.5	12.5
SD	4.69	4.66	4.66	6.14
		$t = 1.732$	$t = 8.66$	$t = 2.635$
		$p = .18$	$p = .003$	$p = .08$
Boston Diagnostic Aphasia Exam				
Animals				
Mean	3.75	5	5	7.5
SD	3.86	3.92	4.32	4.44
		$t = 5.00$	$t = 5.00$	$t = 2.611$
		$p = .02$	$p = .02$	$p = .08$
Boston Diagnostic Aphasia Exam				
Tools/implements				
Mean	3.25	3.5	6	5.75
SD	1.89	2.38	2.94	1.71
		$t = .397$	$t = 3.67$	$t = 8.66$
		$p = .72$	$p = .04$	$p = .003$

4. Discussion

This is the first study to report lasting, improved naming at 2 months and 8 months following application of rTMS in chronic aphasia. The application of 1 Hz rTMS to a portion of R Broca's homologue resulted in significant improvement in naming pictures on the BNT, and in Animals and Tools/Implements subtests

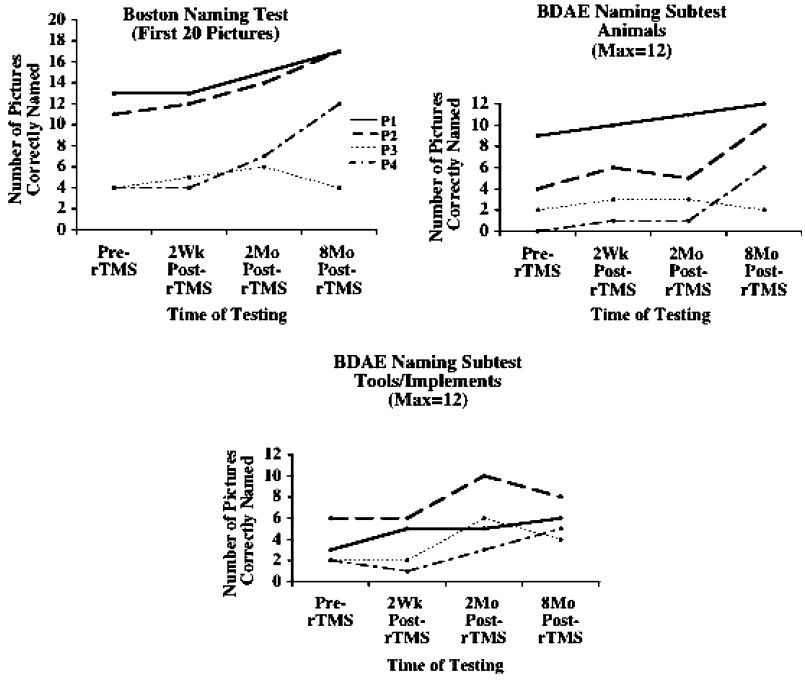

Fig. 4. Naming scores on three standardized language tests pre-rTMS, and at 2 weeks, 2 months, and 8 months after 10 rTMS treatments, for each patient. There was significant improvement on all three naming tests at 2 months post-rTMS (Table 2). Each patient showed improvement over time; and P4, the most severe patient with global aphasia, showed the most dramatic improvement, especially at 8 months post-rTMS.

on the BDAE at 2 months after 10 rTMS treatments. At 8 months after rTMS, there was a significant increase for naming Tools/Implements, and a trend toward significant increase on the BNT, and on Animal Naming on the BDAE ($p = .08$). Three of the four patients demonstrated additional improved scores on these three naming tests at 8 months.

Improvement was also observed in number of words per longest phrase length in elicited, propositional speech for two of the three nonfluent patients when tested with the BDAE at 2 months post-rTMS. The improvements observed in picture naming and phrase length at 2 months post-rTMS suggest that the 2-month period following a series of rTMS treatments might be an optimum time to provide speech therapy for these patients, in order to promote better potential for language improvement.

The sustained improvement for naming, in three of the four patients at 8 months after rTMS suggests that long-term brain re-organization may be taking place or that the rTMS led to a behaviorally beneficial change in speech strategy in our patients. It is unlikely the patients' improved naming scores are related to their having learned the test items, although for some patients this is possible. However, test–retest reliability for picture naming tasks has been shown to be good over repeated test administrations, and practice effects are minimal (Flanagan & Jackson, 1997; Huff, Collins, Corkin, & Rosen, 1986). In a study performed several years ago, Brookshire (1971) observed that repeated trials of naming tests did not result in improved naming performance in patients with aphasia. Our patients were not provided feedback on the BNT, BDAE naming subtests, or the Snodgrass and Vanderwart pictures used in this rTMS study.

Nevertheless, our results should be considered preliminary, as this was an open-protocol study, and no patients received sham rTMS. All patients were in the chronic, stable phase of aphasia, however, and were well beyond the spontaneous recovery period of 3–6 months poststroke (Demeurisse & Capon, 1987). The improvements in the severe aphasia patient (P4) are particularly striking because global aphasia patients are expected to have the least potential for improvement (Rosenbek, LaPointe, & Wertz, 1989) and are among the most difficult to treat (Helm-Estabrooks & Albert, 2004, chap. 23; Kertesz & McCabe, 1977; Sarno & Levita, 1981).

4.1. Role of Broca's area in a neural network for semantic tasks

The participation of Broca's area (pars triangularis and pars opercularis portion of L inferior prefrontal cortex, L IPC) along with posterior temporal lobe structures has been observed in semantic tasks during functional imaging with normals (Gold & Buckner, 2002), as well as aphasia patients (Price et al., 2001). Studies have also demonstrated that L IPC is important for *selection* of competing semantic knowledge (Gabrieli, Poldrack, & Desmond, 1998; Gold & Buckner, 2002).

Thompson-Schill et al. (1998) observed that among aphasia patients with lesion that included the L inferior frontal gyrus (L IFG), there was a direct correlation between extent of lesion within L BA 44, and *selection-related errors* on a task requiring the subject to generate a verb for a written noun. In word-stem completion tasks, aphasia patients with L IFG lesions have been observed to primarily shift activation to the R hemisphere (R IFG, R fusiform, and R lateral occipital cortex) with improved modulation (decreased response) in R-sided structures as performance improved with practice (Blasi et al., 2002).

We hypothesize that in the present study, application of 1 Hz rTMS to an anterior portion of R Broca's homologue (R pars triangularis) suppressed this area. We posit that suppression of the R pars triangularis modulated the prefrontal/temporo-parietal connections important for picture naming. It is likely that suppression of R pars triangularis in these patients promoted better modulation in the RH, as well as remaining LH temporo-parietal language structures important for naming (Bookheimer et al., 1995; Damasio et al., 1996; Friston et al., 1991; Gold & Buckner, 2002; Price et al., 2001). Previous functional imaging studies performed before and after speech therapy, have suggested that new LH activation may be particularly important where good response has been observed (Cornelissen et al., 2003; Leger et al., 2002; Musso et al., 1999; Small et al., 1998). Functional imaging studies performed pre- and post- a series of rTMS treatments would be necessary to better understand possible changes in the bi-hemispheric neural network for naming, post-rTMS. The relative contribution of the LH and/or RH in aphasia recovery is unknown, and functional imaging studies remain necessary.

While it may seem paradoxical to suggest that promoting inhibition in a RH language homologue (anterior portion of R Broca's area, R pars triangularis) would promote improved naming ability or improved speech, there are animal studies and some human case reports which suggest that direct or indirect neural "damage" to specific areas in the central nervous system may result in facilitation of behavioral functions (reviewed in Kapur, 1996). Kapur has labeled this phenomenon "paradoxical functional facilitation (PFF)." PFF is known as the "Sprague effect" in animal studies. For example, new collicular lesions may bring about an improvement in visual functioning following an initial occipital lesion. In humans, there are case studies whereby ambidextrous adults who had stuttered since childhood no longer stuttered, following unilateral brain damage in adulthood (e.g., stroke or head injury), even as soon as 10 days postonset (Helm-Estabrooks, Yeo, Geschwind, Freedman, & Weinstein, 1986). Vuilleumier, Hester, Assal, and Regli (1996) reported the disappearance of left-sided unilateral neglect, brought on by a right parietal infarct, after the occurrence of a new lesion in the area of the left frontal eye field. Hilgetag et al. (2001) applied rTMS to the parietal cortex to demonstrate a similar, paradoxical improvement of attention to ipsilateral targets, and Oliveri et al. (1999) and Brighina et al. (2003) have shown that TMS applied to the healthy hemisphere can reduce hemispatial neglect following a right hemispheric stroke.

5. Conclusions

TMS may provide a novel treatment approach for aphasia. Our results in this open trial support conducting a sham rTMS controlled trial, with overt naming fMRI before, and following a series of rTMS treatments. In addition, a future study should include multiple baseline language testing pre-rTMS, as well as some repeated testing within the post-rTMS testing periods. Importantly, none of our patients had any undesirable side-effects in the present study, thus rTMS appears to be safe in these patients. Indeed, the slow (1 Hz) rTMS frequency used in our study is similar to the slow rTMS frequencies (0.33 and 0.5 Hz) used in seizure studies, where reduced seizures have been observed post-rTMS (Tassinari et al., 2003). Future fMRI studies with aphasia patients before and after a series of rTMS treatments are necessary to examine whether rTMS has altered activation in specific cortical regions of the bi-hemispheric neural network for naming and other language behaviors, thus aiding our understanding of the mechanism of action of rTMS.

Acknowledgments

Research supported by NIH Grant RO1 DC05672, National Institute on Deafness and Other Communication Disorders, Bethesda, MD and a grant from the Medical Research Service, Department of Veterans Affairs, Washington, DC (to M.A.N.); a K24 award (RRO18875, to A.P.-L) and the Harvard–Thorndike General Clinical Research Center (NCRR MO1 RR01032).

References

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B. M., & Zilles, K. (1999). Broca's region revisited: Cytoarchitecture and intersubject variability. *Journal of Comparative Neurology, 412*, 319–341.

Barlow, T. (1877). *British Medical Journal*, 103–104.

Basso, A., Gardelli, M., Grassi, M. P., & Mariotti, M. (1989). The role of the right hemisphere in recovery from aphasia. Two case studies. *Cortex, 25*(4), 555–566.

Belin, P., Van Eeckhout, P., Zilbovicious, M., Remy, P., Francois, C., Guillaume, S., et al. (1996). Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. *Neurology, 47*, 1504–1511.

Berardelli, A., Inghilleri, M., Rothwell, J. C., Romeo, S., Curra, A., Gilio, F., et al. (1998). Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Experimental Brain Research, 122*, 79–84.

Blasi, V., Young, A. C., Tansy, A. P., Petersen, S. E., Snyder, A. Z., & Corbetta, M. (2002). Word retrieval learning modulates right frontal cortex in patients with left frontal damage. *Neuron, 35*, 159–170.

Bookheimer, S. Y., Zeffiro, T. A., Blaxton, R., Baillard, W., & Theodore, W. (1995). Regional cerebral blood flow during object naming and word reading. *Human Brain Mapping, 3*, 93–106.

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., LaBua, V., Daniele, O., et al. (2003). 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neuroscience Letters, 336*, 131–133.

Broca, P. (1861). Remarques sur le siège de la faculté du langage articule, suivies d'une observation d'aphémie (Perte de la Parole). *Bulletin de la Société Anatomique de Paris, 6*, 330–357.

Brookshire, R. (1971). Effects of trial time and inter-trial interval on naming by aphasic subjects. *Journal of Communication Disorders, 3*(4), 289–301.

Calvert, G. A., Brammer, M. J., Morris, R. G., Williams, S. C., King, N., & Matthews, P. M. (2000). Using fMRI to study recovery from acquired dysphasia. *Brain and Language, 71*(3), 391–399.

Cao, Y., Vikingstad, E. M., George, K. P., Johnson, A. F., & Welch, K. M. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke, 30*(11), 2331–2340.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology, 48*, 1398–1403.

Cornelissen, K., Laine, M., Tarkiainen, A., Jarvensivu, T., Marin, N., & Salmelin, R. (2003). Adult brain plasticity elicited by anomia treatment. *Journal of Cognitive Neuroscience, 15*, 444–461.

Czopf, J. (1972). Uber die Rolle der nicht dominanten Hemisphäre in der Restitution der Sprache der Aphasischen. *Archiv fur Psychiatrie und Nervenkrankheiten, 216*, 162–171.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature, 380*(6574), 499–505.

Demeurisse, G., & Capon, A. (1987). Language recovery in aphasic stroke patients: Clinical, CT and CBF studies. *Aphasiology, 1*(4), 301–315.

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. S. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 15*(1), 71–84.

Epstein, C. M., Meador, K. J., Loring, D. W., Wright, R. J., Weissman, J. D., Sheppard, S., et al. (1999). Localization and characterization of speech arrest during transcranial magnetic stimulation. *Journal of Clinical Neurophysiology, 110*, 1073–1079.

Flanagan, J. L., & Jackson, S. T. (1997). Test–retest reliability of three aphasia tests: Performance of non-brain-damaged older adults. *Journal of Communication Disorders, 30*(1), 33–43.

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1991). Investigating a network model of word generation with positron emission tomography. *Proceedings of the Royal Society of London B, 244*, 101–106.

Gabrieli, J. D. E., Poldrack, R. A., & Desmond, J. E. (1998). The role of left prefrontal cortex in language and memory. *Proceedings of the National Academy of Sciences, 95*, 906–913.

George, M. S., & Bellmaker, R. H. (2000). *Transcranial magnetic stimulation in neuropsychiatry*. Washington, DC: American Psychiatric Press.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). *The assessment of aphasia and related disorders* (3rd ed.). Philadelphia, PA: Lippincott, Williams and Wilkins.

Gold, B. T., & Buckner, R. L. (2002). Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron, 35*, 803–812.

Gowers, W. R. (1886). *A manual of diseases of the nervous system*. London: Churchill.

Heiss, W. D., Karbe, H., Weber-Luxenburger, G., Herholz, K., Kessler, J., Pietrzyk, U., et al. (1997). Speech-induced cerebral metabolic activation reflects recovery from aphasia. *Journal of Neurological Sciences, 145*, 213–217.

Heiss, W. D., Kessler, J., Thiel, A., Ghaemi, M., & Karbe, H. (1999). Differential capacity of left and right areas for compensation of poststroke aphasia. *Annals of Neurology, 45*(4), 430–438.

Helm-Estabrooks, N., Yeo, R., Geschwind, N., Freedman, M., & Weinstein, C. (1986). Stuttering: Disappearance and reappearance with acquired brain lesions. *Neurology, 36*, 1109–1112.

Helm-Estabrooks, N., & Albert, M. L. (2004). Cognitive approach to improving auditory comprehension. In *Manual of aphasia and aphasia therapy* (2nd ed., pp. 335–362). Austin, TX: Pro-Ed.

Hilgetag, C. C., Theoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nature Neuroscience, 4*, 953–957.

Huff, F. J., Collins, C., Corkin, S., & Rosen, J. T. (1986). Equivalent forms of the Boston Naming Test. *Journal of Clinical Experimental Neuropsychology, 8*(5), 556–562.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *The Boston Naming Test*. Philadelphia, PA: Lippincott, Williams and Wilkins.

Kapur, N. (1996). Paradoxical functional facilitation in brain-behavior research: A critical review. *Brain, 119*, 1775–1790.

Karbe, H., Thiel, A., & Weber-Luxenburger, G. (1998). Brain plasticity in poststroke aphasia: What is the contribution of the right hemisphere? *Brain and Language, 64*(2), 215–230.

Karbe, H., Thiel, A., Weber-Luxenburger, G., Kessler, J., Herholz, K., & Heiss, W. D. (1998a). Reorganization of the cerebral cortex in post-stroke aphasia studied with positron emission tomography. *Neurology, 50*, A321.

Kauffman, C. D., Cheema, M. A., & Miller, B. E. (2004). Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: A double-blind, placebo-controlled study. Peer-reviewed letter. *Depression and Anxiety, 19*, 59–62.

Kertesz, A., & McCabe, P. (1977). Recovery patterns and prognosis in aphasia. *Brain, 100*, 1–18.

Kim, Y. H., Ko, M. H., Parrish, T. B., & Kim, H. G. (2002). Reorganization of cortical language areas in patients with aphasia: A functional MRI study. *Yonsei Medical Journal, 43*(4), 441–445.

Kinsbourne, M. (1971). The minor cerebral hemisphere as a source of aphasic speech. *Archives of Neurology, 25*(4), 302–306.

Klein, E., Kolsky, Y., Puyerovsky, L. M., Koran, D., Chistyakov, A., & Feinsod, M. (1999). Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: A double-blind sham-controlled pilot study. *Biological Psychiatry, 46*, 1451–1454.

Klein, E., Kreinin, I., Chistyakov, A., Koren, D., Mecz, L., Marmur, S., et al. (1999a). Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: A double-blind controlled study. *Archives of General Psychiatry, 56*(4), 315–320.

Kosslyn, S. M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J. P., & Thompson, W. L., et al. (1999). The role of area 17 in visual imagery: Convergent evidence from PET and rTMS (p. 167-70) [see comments] [published erratum appears in *Science, 284(5416)*, 197]. *Science, 284*.

Lazar, R. M., Marshall, R. S., Pile-Spellman, J., Duong, H. C., Mohr, J. P., Young, W. L., et al. (2000). Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. *Neuropsychologia, 38*, 1325–1332.

Leger, A., Demonet, J. F., & Ruff, S. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: An fMRI study. *NeuroImage, 17*, 174–183.

Maeda, F., Keenan, J. P., Tormos, J. M., Topka, H., & Pascual-Leone, A. (2000). Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology, 111*, 800–805.

Miura, K., Nakamura, Y., & Miura, F. (1999). Functional magnetic resonance imaging to word generation task in a patient with Broca's aphasia. *Journal of Neurology, 246*, 939–942.

Mottaghy, F. M., Hungs, M., Brugmann, M., Sparing, R., Boroojerdi, B., Foltys, H., et al. (1999). Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology, 53*, 1806–1812.

Mottaghy, F. M., Gangitano, M., Sparing, R., Krause, B. J., & Pascual-Leone, A. (2002). Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. *Cerebral Cortex, 12*(4), 369–375.

Musso, M., Weiller, C., Kiebel, S., Muller, S. P., Bulau, P., & Rijntjes, M. (1999). Training-induced brain plasticity in aphasia. *Brain, 122*, 1781–1790.

Naeser, M. A., Palumbo, C. L., Helm-Estabrooks, N., Stiassny-Eder, D., & Albert, M. L. (1989). Severe non-fluency in aphasia: Role of the medial subcallosal fasciculus plus other white matter pathways in recovery of spontaneous speech. *Brain, 112*, 1–38.

Naeser, M., Theoret, H., Kobayashi, M., Martin, P., Nicholas, M., & Baker, E., et al. (2002). Modulation of cortical areas with repetitive transcranial magnetic stimulation to improve naming in nonfluent aphasia [Abstract #133]. In *Proceedings of the 8th international conference on functional mapping of the human brain*, June 2–6, 2002, Sendai, Japan. Available on CD-Rom in *NeuroImage, 16* (2).

Naeser, M. A., Martin, P. I., Baker, E. H., Hodge, S. M., Sczerzenie, S. E., Nicholas, M., et al. (2004). Overt propositional speech in chronic nonfluent aphasia studied with the dynamic susceptibility contrast fMRI method. *NeuroImage, 22*, 29–41.

Oliveri, M., Rossini, P. M., Traversa, R., Cicinelli, P., Filippi, M. M., Pasqualetti, P., et al. (1999). Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. *Brain, 122*, 1731–1739.

Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., Greenberg, B. D., et al. (1999). Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractive major depression: Comparative study of fast, slow and sham rTMS. *Psychiatry Research, 88*, 163–171.

Pascual-Leone, A., Gates, J. R., & Dhuna, A. (1991). Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology, 41*(5), 697–702.

Pascual-Leone, A., Tormos, J. M., Keenan, J., Tarazona, F., Canete, C., & Catala, M. D. (1998). Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology, 15*, 333–343.

Pascual-Leone, A., Valls-Sole, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain, 117*, 847–858.

Perani, D., Cappa, S. F., Tettamanti, M., Rose, M., Scifo, P., Miozzo, A., et al. (2003). A fMRI study of word retrieval in aphasia. *Brain and Language, 85*, 357–368.

Price, C. J., Warburton, E. A., Moore, C. J., Frackowiak, R. S. J., & Friston, K. J. (2001). Dynamic diaschisis: Anatomically remote and context-sensitive human brain lesions. *Journal of Cognitive Neuroscience, 13*(4), 419–429.

Robertson, E., Tormos, J. M., Maeda, F., & Pascual-Leone, A. (2001). The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. *Cerebral Cortex, 11*, 628–635.

Romero, J. R., Anshel, D., Sparing, R., Gangitano, M., & Pascual-Leone, A. (2002). Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clinical Neurophysiology, 113*(1), 101–107.

Rosen, H. J., Petersen, S. E., Linenweber, M. R., Snyder, A. Z., White, D. A., Chapman, L., et al. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology, 55*, 1883–1894.

Rosenbek, J. C., LaPointe, L. L., & Wertz, R. T. (1989). *Aphasia: A clinical approach*. Austin, TX: Pro-Ed.

Roth, B. J., Saypol, J. M., Hallett, M., & Cohen, L. G. (1991). A theoretical calculation of the field induced in the cortex during magnetic stimulation. *Electroencephalography and Clinical Neurophysiology, 81*, 47–56.

Sarno, M. T., & Levita, E. (1981). Some observations on the nature of recovery in global aphasia after stroke. *Brain and Language, 13*, 1–12.

Siebner, H. R., Tormos, J. M., Ceballos-Baumann, A. O., Auer, C., Catala, M. D., Conrad, B., et al. (1999). Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology, 52*, 529–537.

Small, S. L., Flores, D. K., & Noll, D. C. (1998). Different neural circuits subserve reading before and after therapy for acquired dyslexia. *Brain and Language, 62*, 298–308.

Snodgrass, J., & 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 and Memory, 6*(2), 74–215.

Tassinari, C. A., Cincotta, M., Zaccara, G., & Michelucci, R. (2003). Transcranial magnetic stimulation and epilepsy. *Clinical Neurophysiology, 114*(5), 777–798.

Tergau, F., Naumann, U., Paulus, W., & Steinhoff, B. J. (1999). Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. *Lancet, 353*, 2209.

Theoret, H., Haque, J., & Pascual-Leone, A. (2001). Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans. *Neuroscience Letters, 306*, 29–32.

Thompson-Schill, S. L., Swick, D., Farah, M. J., D'Esposito, M., Kan, I. P., & Knight, R. T. (1998). Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proceedings of the National Academy of Sciences, 95*, 15855–15860.

Thulborn, K. R., Carpenter, P. A., & Just, M. A. (1999). Plasticity of language-related brain function during recovery from stroke. *Stroke, 30*(4), 749–754.

Vuilleumier, P., Hester, D., Assal, G., & Regli, F. (1996). Unilateral spatial neglect recovery after sequential strokes. *Neurology, 46*(1), 184–189.

Warburton, E., Price, C., & Swinburn, K. (1999). Mechanisms of recovery from aphasia: Evidence from positron emission tomography studies. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*, 155–161.

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Muller, S., Bier, D., et al. (1995). Recovery from Wernicke's aphasia: A positron emission tomographic study. *Annals of Neurology, 37*, 723–732.