Overt naming fMRI pre- and post-TMS: Two nonfluent aphasia patients, with and without improved naming post-TMS

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Abstract
Two chronic, nonfluent aphasia patients participated in overt naming fMRI scans, pre- and post-a series of repetitive transcranial magnetic stimulation (rTMS) treatments as part of a TMS study to improve naming. Each patient received 10, 1-Hz rTMS treatments to suppress a part of R pars triangularis. P1 was a ‘good responder’ with improved naming and phrase length; P2 was a ‘poor responder’ without improved naming.

Pre-TMS (10 years poststroke), P1 had significant activation in R and L sensorimotor cortex, R IFG, and in both L and R SMA during overt naming fMRI (28% pictures named). At 3 mo. post-TMS (42% named), P1 showed continued activation in R and L sensorimotor cortex, R IFG, and in R and L SMA. At 16 mo. post-TMS (58% named), he also showed significant activation in R and L sensorimotor cortex mouth and R IFG. He now showed a significant increase in activation in the L SMA compared to pre-TMS and at 3 mo. post-TMS (p < .02; p < .05, respectively). At 16 mo. there was also greater activation in L than R SMA (p < .08).

At 46 mo. post-TMS (42% named), this new LH pattern of activation continued. He improved on the Boston Naming Test from 11 pictures named pre-TMS, to scores ranging from 14 to 18 pictures, post-TMS (2–43 mo. post-TMS). His longest phrase length (Cookie Theft picture) improved from three words pre-TMS, to 5–6 words post-TMS.

At 3 and 6 mo. post-TMS, there was no longer significant activation in R IFG, but significant activation was present in R sensorimotor cortex. On all three fMRI scans, P2 had significant activation in both the L and R SMA. There was no new, lasting perilesional LH activation across sessions for this patient. Over time, there was little or no change in his activation. His naming remained only at 1–2 pictures during all three fMRI scans. His BNT score and longest phrase length remained at one word, post-TMS.

Lesion site may play a role in each patient’s fMRI activation pattern and response to TMS treatment. P2, the poor responder, had an atypical frontal lesion in the L motor and premotor cortex that extended high, near brain vertex, with deep white matter lesion near L SMA. P2 also had frontal lesion in the posterior middle frontal gyrus, an area important for naming (Duffau et al., 2003); P1 did not. Additionally, P2 had lesion inferior to and posterior to Wernicke’s area, in parts of BA 21 and 37, whereas P1 did not.

The fMRI data of our patient who had good response following TMS support the notion that restoration of the LH language network is linked in part, to better recovery of naming and phrase length in nonfluent aphasia.

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1. Introduction

Brain re-organization supporting recovery of language in aphasia remains unclear. Both the left hemisphere (LH) and the right hemisphere (RH) are thought to support language recovery after stroke (Crosson et al., 2007; Gold & Kertesz, 2000; Price & Crinion, 2005; Thompson, 2000). The exact nature of the contribution from each hemisphere is still debated. Factors including time poststroke when patients are studied (acute or chronic), lesion location and the specific language tasks examined may affect the mechanisms involved in recovery (Price & Crinion, 2005; Thiel et al., 2006).

Since the 1870s, some reports have suggested that the RH can support some recovery of language after LH stroke (Barlow,
2. Transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) allows painless, noninvasive stimulation of the cortex. It utilizes magnetic fields to create electrical currents in cortical regions of interest (ROIs). Repetitive TMS can be used to produce changes in cortical excitability (Lefaucheur, 2006). When rTMS is delivered to the same cortical region at 1 Hz, it generally decreases cortical excitability (Lefaucheur, 2006). When rTMS is delivered to the targeted RH ROI in nonfluent aphasia, would have an overall modulating effect on elements of the distributed neural network for picture naming, resulting in behavioral improvement.

In the present study, we report serial, overt naming functional MRI (fMRI) studies, pre- and post-10, 20-min, 1-Hz rTMS treatments to suppress part of the R PTr, in two chronic nonfluent aphasia patients. One patient was considered ‘a good responder’ to TMS treatment with improved naming at 2 mo. post-treatment, which has lasted almost 4 years. The other patient was considered a ‘poor responder’, with no change in naming post-TMS.

We hypothesized that over time, in patients who have a good response to TMS, during overt naming fMRI, there would be a gradual shift to increased LH activation in perilesional language areas and the L SMA. We further hypothesized that during overt naming fMRI, in patients who have a poor response to TMS, there would be little or no change in LH perilesional activation.

3. Methods

3.1. Participants

Two chronic nonfluent aphasia patients participated in overt naming fMRI studies, pre- and post-TMS treatments, where part of the R PTr was suppressed with rTMS. Patient 1 also participated in overt propositional speech/story-telling fMRI post-TMS. Institutional Review Board approval and signed informed consent were obtained.

3.2. Patient 1, good responder

Patient 1 (P1) was a R-handed engineer who had an L MCA stroke at age 48; he had a moderate R hemiparesis. Fig. 1a shows the structural T1-weighted MRI for this patient. At 10 years post-stroke, P1 was treated with rTMS. At Entry, he had mild-moderate nonfluent speech, with a three-word longest phrase length (Cookie Theft picture, BDAE) (Goodglass, Kaplan, & Barresi, 2001) (Table 1a).

3.3. Patient 2, poor responder

Patient 2 (P2) was a R-handed high school teacher who had a LH stroke at age 56; he had no R hemiparesis. He had an embolic stroke; the stroke etiology was a patent foramen ovale. He was treated with tissue plasminogen activator (tPA), a blood-clot dissolving agent used with stroke patients in the acute setting. Fig. 1b shows the structural T1-weighted MRI for this patient. At 2 years poststroke, P2 was treated with rTMS. At Entry, he was considered to have severe nonfluent speech, with a one-word longest phrase length (Cookie Theft picture, BDAE) (Table 1b).

3.4. Lesion sites in P1 and P2

P1 and P2 each had lesion in the two subcortical white matter areas associated with lasting, nonfluent propositional speech, see Fig. 1c (Duffau et al., 2002; Naeser, Palumbo, Helm-Estabrooks, Stiassny-Eder, & Albert, 1989): (1) medial subcallosal fasciculus (MSFC) area, anterolateral to L frontal horn, deep to Broca’s area; plus (2) periventricular white matter (PVWM) area, lateral to body of lateral ventricle, deep to sensory-motor cortex, mouth. P2 had more lesion in the MSFC area, than P1; however, P2 had less lesion in the PVWM area, than P1. The absence of paralysis in P2 was compatible with this sparing of the deepest PVWM efferent and afferent pathways, adjacent to body of lateral ventricle, see Fig. 1b and c. P1 had a moderate-severe R paralysis with a more extensive PVWM lesion adjacent to body of lateral ventricle, see green arrow and circle in Fig. 1a and c.
P2 had an atypical LH frontal lobe lesion, where lesion in the motor and premotor cortex areas extended high, near the brain vertex, with deep white matter lesion extension near the L SMA (Figs. 1b and 2). The atypical lesion distribution in P2 may have been related to use of tPA in his case. This high portion of his lesion may have undercut additional fibers that course from the SMA.
<table>
<thead>
<tr>
<th>Time poststroke</th>
<th>Max</th>
<th>BDAE subtest animals</th>
<th>BDAE subtest tools/implements</th>
<th>Longest number of words per phrase length (Cookie Theft picture)</th>
<th>Auditory comprehension</th>
<th>Repetition</th>
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<tr>
<td>2 mo. Post-rTMS</td>
<td>58</td>
<td>14</td>
<td>5</td>
<td>5</td>
<td>75.7</td>
<td>5</td>
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<tr>
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<td>59</td>
<td>18</td>
<td>10</td>
<td>4</td>
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<td>6</td>
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<tr>
<td>8 mo. Post-rTMS</td>
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<td>17</td>
<td>10</td>
<td>8</td>
<td>77.3</td>
<td>6</td>
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<tr>
<td>16 mo. Post-rTMS</td>
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<td>15</td>
<td>7</td>
<td>6</td>
<td>52.8</td>
<td>11</td>
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<tr>
<td>43 mo. Post-rTMS</td>
<td>62</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>68</td>
<td>13</td>
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4. Language outcome measures

Prior to any TMS, language testing included the first 20 pictures on the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 2001) and selected subtests from the Boston Diagnostic Aphasia Exam (BDAE) (Goodglass et al., 2001). The primary outcome measures following a TMS treatment series were the BNT, the category naming subtests from the BDAE, and the number of words per longest phrase length (Snodgrass & Vanderwart, 1980) pictures was established at Entry, for each patient. The baseline mean response time (RT) and the mean number of S&V pictures named correctly across the lists were calculated.

Each patient was requested not to receive any individualized speech therapy throughout the first year of the study. However, at approximately 4 mo. post-Phase 2 rTMS, P2 was given a hand-held augmentative speech device by his speech-language pathologist. He was facile with using the device and it appeared that his own attempts at verbalization became reduced after using this device (personal observation). P1, entered into a Constraint-Induced Aphasia Treatment Program (CIAT), which emphasized verb production (Goral & Kempler, 2008), at 24 mo. post-TMS (12 years poststroke), within a year after the overt naming fMRI session at 16 mo. post-TMS, prior to the overt naming fMRI session at 46 mo. post-TMS.

4.2. Imaging sessions

A 3-Tesla MRI scanner (Philips, Intera) at the Boston University Center for Biomedical Imaging (BU CBI) was used to acquire structural and functional imaging. Structural MRI and overt naming fMRI were acquired prior to TMS treatment and in follow-up sessions beginning at 3 mo. after the TMS treatment series was completed. P1 also participated in overt propositional speech/story-telling fMRI, post-TMS.

4.3. Structural MRI

Acquisition parameters for the 3D magnetization prepared rapid gradient echo (MPRAGE) structural images were as follows: TR = 6.85, TE = 3.2, matrix size 256 × 256, FOV 256, number of slices = 125, slice thickness = 1.20 mm. Images were acquired in the sagittal view and re-sliced into the axial plane. Fig. 1 presents the 3D MPRAGE MRI scans for P1 and for P2.

4.4. Functional MRI

Acquisition parameters for the overt speech fMRI scans were as follows: TR = 3000 ms, TE = 35 ms, matrix size 128 × 128, FOV 256, number of slices = 34, slice thickness = 4 mm. Images were acquired in the axial plane.

4.5. Overt naming fMRI block design paradigm

Overt naming fMRIs were obtained and analyzed in the same manner as Martin et al., 2005. Fig. 3a shows the schematic diagram of the continuous sample, block design for overt naming fMRI. The continuous sample, block design, overt naming fMRI paradigm that was utilized took advantage of the hemodynamic response delay where increased blood flow remains for 4–8 s after the task (Friston, Jezzard, & Turner, 1994). Therefore, task-related information is obtained after the task, minimizing motion artifact (Barch et al., 1999; Birn, Cox, & Bandettini, 2004; Eden, Joseph, Brown, Brown, & Zeffiro, 1999).

Images were modeled using a box-car reference function for the block design, which consisted of two alternating conditions: silent viewing of black and white patterns (control condition) and overt picture naming. Sixty pictures were presented from the S&V database of black and white line drawings (Snodgrass & Vanderwart, 1980).

There were two runs (30 different pictures, each run) with 104 image volumes. Each run consisted of 10 epochs each, of pattern (silent) or picture (overt speech) conditions, for a total of 20 epochs. An additional pattern epoch was included at the beginning of the run, but was not included in the statistical analyses. Each
pattern or picture was presented for 5 s and was preceded by a 1-s fixation dot for a total trial time of 6 s. The pattern epochs consisted of two patterns, lasting 12 s each (four image volumes), and alternated with picture (overt speech) epochs consisting of three pictures, lasting for 18 s (six image volumes). Each run lasted 5 min 12 s, with a short break given between runs.

Most words were monosyllabic and presentation was pseudorandomized so that no two consecutive stimuli began with the same phoneme or belonged to the same semantic category. Stimuli were projected onto a backlit screen and each participant viewed them through a mirror located over the head in the scanner. A noise-reduction acoustical microphone and headset (FOMRI; Phone-Or Ltd., Or Yehuda, Israel) were used, and the verbal responses were transmitted to and recorded with sound filtering software on a laptop computer in the MRI control room. Overt responses were transcribed at the time of scanning, and available later, from the recorded output. Prior to participation, subjects were trained on a set of practice pictures (not shown during scanning), outside the scanner on an iMac G4 for up to three visits, and on the mock MRI scanner at the BU CBI.

4.6. Overt propositional speech fMRI block design paradigm

Only P1, who had mild-moderate nonfluent speech, participated in overt propositional speech/story-telling fMRI. P2, who had severe nonfluent speech (one-word phrase length), was considered too severe for participation in the overt propositional speech/story-telling paradigm.

The continuous sample, block design for overt propositional speech was similar to the overt naming block design and consisted of two alternating conditions: silent viewing of black and white patterns (control condition), and overt propositional speech (picture description/story-telling). Pictures were black and white line drawings that depicted a story (four sequential pictures per story) (Naeser et al., 2004). Each picture was on the screen for 9 s (see schematic in Fig. 3b). Two pictures were presented per epoch. Two epochs of propositional speech made a complete story. There were two runs of 104 image volumes. Each run lasted 5 min 12 s, with a short break between runs.

4.7. fMRI analyses

Analyses were completed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Post-processing of the images included: (1) motion-correction, using a rigid body 6-parameter realignment algorithm where the first image after the dummy scans was used as a reference; (2) realignment and co-registration to the 3D MPRAGE scan of all time series scans; (3) spatial normalization of the 3D MPRAGE scan to the MNI T1 template image where the resulting spatial transformation parameters were then applied to the EPI time series; and (4) smoothing of the EPI time series with a 6-mm FWHM Gaussian filter. The size of the voxels after normalization was $2 \times 2 \times 2 \, \text{mm}^3$.

The fMRI data were considered acceptable if the amount of motion after correction was within a range of less than 0.5 mm in any direction across a run of 104 images. The amount of motion for each patient fell within an acceptable range and no data for these patients were excluded.

As shown in Fig. 3, at the beginning of each silent 12-s pattern epoch, there continued to be approximately 6 s of hemodynamic response from overt speech (hemodynamic delay naming, hdN). The first 6 s of the pattern condition could then be compared to the last 6 s of the pattern condition. A t-contrast of overt speech (hdN) compared to pattern was set up to determine task-related functional activation.

Analysis was initially completed with a whole brain analysis method. A threshold for signal amplitude of $p < 0.001$ (uncorrected) and $p < 0.05$ (corrected at the cluster level using Family-Wise Error) (Worsley et al., 1996) was utilized. Statistical t-maps showing functional activation at the corrected level for the whole brain were superimposed on the matched structural images using MRicro software (Rorden & Brett, 2000).

In addition, in order to perform statistical comparisons of pre- and post-TMS fMRI sessions for each patient, we completed an ROI analysis that computed the mean effect size, using the MarsBaR toolbox within SPM99 (Brett, Anton, Valabregue, & Poline, 2002). This avoids threshold effects when making comparisons from one session to another in an individual patient. Other methodologies exist for examination of fMRI activation over time, across multiple sessions, such as intra-class correlation coefficient (ICC), but they are often utilized in group studies to examine between-subject and within-subject effects, not individual case studies (Meltzer, Postman-Caucheteux, McArdle, & Braun, 2009). Such studies examining magnitude of signal change may be useful for group studies, but caution should be taken when examining within-subject effects (Chee, Lee, Soon, Westphal, & Venkatraman, 2003).

ROIs were chosen to encompass the following regions within the neural network for naming including R IFG (PTr and POp); R sensorimotor cortex; and the L and R SMA for both patients. We also examined L sensorimotor cortex for P1. P2 had extensive lesion in this region, which did not allow us to create a L sensorimotor cortex ROI. All ROIs were identified using anatomical landmarks (see below), hand drawn on each patient’s individual, normalized brain in MRicro and then converted to analyze format for use in the MarsBaR toolbox.

The location of the R IFG (which included both the POp and PTr) was defined by the following anatomical landmarks: (1) inferior frontal sulcus, dorsal border; (2) Sylvian fissure, inferior border; (3) inferior precentral sulcus, posterior border for POp; and (4) horizontal ramus, anterior border of PTr (Amunts et al., 1999, 2004;
The location of the single, best RH cortical ROI to suppress with rTMS to improve picture naming was determined individually for each patient. During this phase, 1-Hz rTMS was applied at 90% of motor threshold (for L FDI) for 10 min, using a 8-shaped TMS coil (7 cm diameter), which directly affected a cortical target about 1 cc in size (see Fig. 4). This rTMS protocol was applied in separate sessions, to four different RH cortical ROIs. These included: M1, mouth (orbicularis oris, verified with motor evoked potential); and three subregions within Broca’s area: PTr anterior, PTr posterior, and POp, as defined below.

Broca’s area is classically defined as the PTr and POp portions of the inferior frontal gyrus (IFG). Although PTr and POp are sometimes considered to represent BA 45 and BA 44, respectively, only cytoarchiteconic studies from post-mortem brain examination can determine the borders that define these Brodmann areas.

The subregions within Broca’s area become more complex when a diagonal sulcus is present. A RH diagonal sulcus was present for each patient in this study. The diagonal sulcus is located caudal to the vertical ascending ramus, within the IFG (see Fig. 5c). Amunts et al. (2004) observed in a study where structural MRI and cytoarchitectonics were examined in the same 10 brains, that a diagonal sulcus was present in only every second hemisphere. They observed that the diagonal sulcus could either mark the border between BA 44 and 45 or it could be inside BA 44. Although it is understood that without cytoarchitectonics, it was not possible to know whether the diagonal sulcus was a border between POp and PTr or if it was within POp, in the present study it was used to delimit POp from PTr for each case.

The location of PTr and POp were identified on each patient’s brain using the following anatomical landmarks (sulcal and gyral boundaries): (1) POp: gyrus that is rostral to the inferior precentral sulcus and caudal to the diagonal sulcus; (2) PTr posterior: gyrus that is rostral to the diagonal sulcus and caudal to the vertical ascending ramus; (3) PTr anterior: gyrus that is rostral to the triangular sulcus and caudal to the horizontal ramus (Amunts et al., 1999; Amunts et al., 2004; Anwander et al., 2006; Keller et al., 2007; Nishitani et al., 2005) (see Fig. 5c).

The S&V picture naming was tested immediately before, and after, each ROI was suppressed with 10 min of 1-Hz rTMS. The single RH cortical ROI associated with at least a two SD improvement above Baseline S&V naming obtained at Entry (see Methods, Baseline Testing, p. 10), immediately following 10 min of rTMS, was considered to be the Best Response RH cortical ROI for that patient. The Best Response RH ROI for P1 was the PTr posterior, where he named 15 pictures post-TMS (baseline mean S&V = 10.59, SD = 1.87, +2 SD = 14.33). The Best Response RH ROI for P2 was the PTr anterior, where he named three pictures post-TMS (baseline mean S&V = 0.9, SD = 0.567, +2 SD = 2.035). Fig. 5 shows the location of each Best Response RH ROI for each patient. Immediate post-TMS testing for each of the other three ROIs did not reach criterion for Best Response.

5.2. Phase 2 rTMS, suppress best response RH ROI longer, over more sessions

During Phase 2, the Best Response ROI from Phase 1 was suppressed with 1-Hz rTMS (90% of motor threshold for the L FDI) for 20 min, 5 days per week, across 2 weeks. Each patient received
6. Results

6.1. Language data (P1, good responder)

For P1, language was tested at 2, 6, 16, and 43 mo. post-Phase 2 rTMS (Table 1a). The BNT score increased from 11 pictures named (pre-TMS) to 14, 18, 15, and 15 (post-TMS), Fig. 6a. The number of words for longest phrase (Cookie Theft picture, BDAE) increased from three words (pre-TMS) to 5, 5, 5, and 6 words, respectively (post-TMS). Auditory comprehension was largely unchanged.

6.2. Overt naming fMRI (P1)

Pre-TMS, P1 named only 17/60 (28%) of the pictures during overt naming fMRI (10 years poststroke). At that time, fMRI ROI analyses showed significant activation in the R and L sensorimotor cortex and R IFG. At 3 mo. post-TMS he named 25/60 (42%) of the pictures and ROI analyses showed continued significant activation in both the R and L sensorimotor cortex. At 16 mo. post-TMS his naming improved to his highest score of 35/60 (58%) and the ROI analyses showed increased activation in both R and L sensorimotor cortex, mouth. Increased activation in the L (perilesional) and R sensorimotor cortex, mouth, continued to be present at 46 mo. post-TMS. Although ROI analyses showed there was increased activation over time in the R and L sensorimotor cortex, mouth, the change in activation did not reach a level of significant change over time (see Figs. 7 and 8).

ROI analyses also showed that pre-TMS, there was significant activation in both the L and R SMA. At 3 mo. post-TMS, this activation continued to be present. The mean effect size for the L SMA was significantly greater at 16 mo. post-TMS compared to pre-TMS and 3 mo. post-TMS (p < .02; p < .05, respectively). There was no significant change over time in the R SMA. At 16 and 46 mo. post-TMS there was greater activation in L SMA than R SMA (p < .08; p < .09, respectively) (see bar graph, Fig. 7).

At 16 mo. post-TMS whole brain analyses showed there was new perilesional L frontal activation in the middle portion of the lateral, superior frontal gyrus (SFG) (L BA 8), and new temporal activation in L and R BA 20, R BA 22 and 37. The perilesional activation in the middle portion of the lateral L SFG (L BA 8) was present at both 16 and 46 mo. post-TMS.

6.3. Overt propositional speech fMRI (P1)

Only P1 participated in overt propositional speech/story-telling fMRI and this occurred at 16 and 46 mo. post-TMS. On both of these post-TMS fMRI scans during overt story-telling, the whole brain analyses for P1 showed perilesional activation in a small remaining portion of L IFG, and in L sensorimotor cortex, mouth.
ROI analyses at 16 mo. post-TMS showed there was significant activation in L and R SMA (Fig. 9, bar graphs). At 46 mo. post-TMS there continued to be significant activation in only the L SMA. His longest phrase length for propositional speech during the fMRI scan at 16 mo. post-TMS was three words (e.g., Wait a minute; The fan blowin’) and during the fMRI scan at 46 mo. post-TMS, five words (e.g., Look at him get busy).

6.4. Overt propositional speech DSC fMRI paradigm

During an earlier fMRI research project, 6 years pre-TMS (4 years poststroke) P1 participated in an overt propositional speech/story-telling imaging study. That study utilized gadolinium with the Dynamic Susceptibility Contrast (DSC) fMRI method to obtain data on relative cerebral blood volume in specific cortical ROIs (Naeser et al., 2004). The sequential pictures used as stimuli for story-telling during DSC fMRI, were the same pictures used later, during the overt propositional speech fMRI studies at 11 years 5 mo. poststroke; and 13 years 11 mo. poststroke. During DSC fMRI, he had produced only a two-word longest phrase length (e.g., get up, bed) for the picture description/story-telling task. At that time, P1 showed greater activation in R SMA than in L SMA (Fig. 10, white arrows).

6.5. Language data (P2, poor responder)

Pre-TMS, language testing was performed three times with P2 (1.5 years poststroke). At that time, his BNT scores were 1, 3, and 1 (mean = 1.67; SD = 1.15), and his longest phrase length was one word (cookie theft, BDAE). Auditory comprehension for Commands was 8, 10, and 8 (mean = 8.67; SD = 1.15). At 2 and 6 mo. post-Phase 2 rTMS, his BNT score was only one picture named, and his longest phrase length remained at one word. Auditory comprehension for Commands improved by 2 SD, from a pre-TMS mean of 8.67 to 11. Auditory comprehension for Complex Ideational Material also improved by 2 SD, from pre-TMS mean, 2.33 (SD = 0.58) to 4, at 6 mo. post-TMS (see Table 1b for additional language data).

6.6. Overt naming fMRI (P2)

Pre-TMS, P2 named only 2/60 pictures and the ROI analyses showed significant activation in R IFG. At 3 and 6 mo. post-Phase 2 rTMS, there was little activation in the R IFG. The ROI analyses revealed no significant difference in R IFG activation across sessions and additionally, no significant change in the R sensorimotor activation across all three sessions. This corresponds to no change in
the number of pictures named during the fMRI scans (see Figs. 11 and 12, bar graphs).

On all three overt naming fMRI scans (pre-TMS, and at 3 and 6 mo. post-TMS), ROI analyses showed no difference across sessions in activation for the L or R SMA. Although more activation was seen in the L SMA compared to the R SMA, this difference did not reach a level of significant difference in activation in the L SMA compared to R SMA in this patient (see bar graph, Fig. 11).

Pre-TMS there had been activation in a portion of L BA 37. This did not remain across sessions. At 3 mo. post-TMS, there was new activation in L anterior STG, and in L BA 38. At 6 mo. post-TMS however, no L temporal lobe activation was present any longer. Across all three sessions, pre- and post-TMS in this patient, whole brain analyses revealed activation in the middle portion of L lateral SFG (L BA 8). However, there was no new, lasting LH perilesional or perisylvian activation post-TMS and no improvement in naming.

7. Discussion

This study reported results for overt naming fMRI scans, pre- and post-10, 20-min, 1-Hz rTMS treatments to suppress part of R PTr, in two chronic nonfluent aphasia patients. One patient was a ‘good responder’ with improved naming and phrase length in propositional speech, lasting out to almost 4 years post-TMS. The other patient was a ‘poor responder’ with no change in naming or propositional speech post-TMS.
We had hypothesized that in chronic nonfluent aphasia, after rTMS treatment to suppress R PTr, fMRI would show a shift in activation from RH frontal areas to new activation in LH perilesional, perisylvian areas and L SMA, if there was good response with improved naming. For P1, who was a ‘good responder’, at 16 mo. post-TMS, there was significant activity in LH perilesional sensorimotor cortex activation. For P1, significant activation in L sensorimotor cortex continued to be present at 46 mo. post-TMS, with continued improved naming.

In addition, at 16 mo. post-TMS, there was a significant increase in activation in the L SMA compared to pre- and 3 mo. post-TMS (p < .02; p < .05, respectively). There was also greater activation in L SMA than R SMA at 16 mo. post-TMS, whereas pre-TMS there had been no difference between L and R SMA activation. It is unknown exactly when, post-TMS, the shift to the stronger LH activation occurred for this patient during overt naming; however, it was first observed at 16 mo. post-TMS. There were no interovert speech fMRI scans between 3 and 16 mo. post-TMS. The new LH activation remained, however, even at 46 mo. post-TMS (nearly 4 years post-TMS) when the patient was 13 years 11 mo. poststroke.

Overt story-telling fMRI obtained for P1 only, at 16 and 46 mo. post-TMS, showed significant activation in L and R sensorimotor cortex mouth and significant activation in L and R SMA. However, at 46 mo. post-TMS, ROI analyses showed activation in the SMA remained significant for the L SMA only. Data showing greater R than L SMA activation had been obtained for P1 during overt story-telling DSC fMRI, 6 years prior to any TMS. These DSC fMRI data suggest that this patient had greater RH activation at least as early as 4 years poststroke.

For P2, who was a ‘poor responder’, suppression of R PTr with rTMS resulted in no lasting change in LH activation during overt naming fMRI, corresponding with no change in naming or propositional speech post-TMS. Pre-TMS, P2 showed activation in R IFG and R sensorimotor cortex mouth. At 3 and 6 mo. post-TMS, there was continued activation in these ROIs. However, ROI analyses showed there was no difference across sessions in the activation of the R IFG, or R sensorimotor cortex.

On all three fMRI scans (pre-TMS, and at 3 and 6 mo. post-TMS), ROI analyses also showed no difference across sessions in the L or R SMA activation. P2 had severe damage to parts of the neural network important for propositional speech, as well as damage to parts of the neural network important for naming. A discussion of lesion sites in both patients, follows below.

7.1. Lesion sites

Each patient had extensive lesion in Broca's area (Fig. 1), however, presence of lesion in Broca's area, alone, would not have accounted for the lasting nonfluently speech in each case, nor for the discrepancy in severity of nonfluent speech between the two cases.

P2 continued to name only one picture on the BNT, post-TMS. He had an unusually high, frontal lobe lesion, which is important to consider regarding his severe impairment in picture naming. First, this high frontal lobe lesion may have interrupted MSc pathways close to their origin, the SMA, contributing to his limited speech output.

Second, P2 had lesion in an ‘epicenter’ for naming at the junction of the superior frontal sulcus with the precentral sulcus (Duffau et al., 2003, 2005) which may have interrupted connections in the neural network for naming to and from this region.

In addition to differences in their frontal lobe lesion pattern, P1 and P2 had differences in temporal lobe lesion, which may further explain their disparity in picture naming ability. Although each case had lesion in Wernicke's area (posterior STG), P2 had additional lesion extension inferior and posterior to Wernicke's area, including parts of MTG (BA 21 and 37) whereas P1 did not. Several imaging studies have noted the importance of BA 21 and/or BA 37 for semantic aspects of naming in normals as well as aphasia patients (Abrahams et al., 2003; Gold & Buckner, 2002; Hillis et al., 2006; Price, Warburton, Moore, Frackowiak, & Friston, 2001).

Thus, for P2, the severe naming deficit (and poor response following TMS) may have been associated with lesion in two major ‘epicenters’ for naming, as described by Duffau et al. (2003, 2005): (1) DLpFC in posterior MFG at the junction of the superior frontal sulcus and the precentral sulcus; and (2) the MTG (BA 21). In addition, Price et al. (2001) described functional imaging co-activation between Broca's area and the posterior MTG during naming. Thus, the severe anoma (and poor response to TMS) in P2 is likely associated with having lesion in Broca's area plus the two areas described by Duffau et al. (2003, 2005).

Connections from the temporal lobe to Broca's area and precentral gyrus (BA 6) have been reported in recent DTI studies (Frey, Campbell, Pike, & Petrides, 2008; Glasser & Rilling, 2008). White matter lesion was also likely present in fiber bundles connecting these critical regions including the inferior fronto-occipital fasciculus and the arcuate fasciculus (Catani, Jones, & ffytche, 2005; Duffau et al., 2005). Further studies with DTI, particularly in aphasia patients, would be necessary to better understand these disconnections.
P1 had no lesion in the L MTG (BA 21 and 37), or the posterior MFG (a part of BA 8). Interestingly, P1 showed no consistent activation in these LH regions during overt naming fMRI. Although he showed no activation in the posterior portion of the L MFG, he
did activate other parts of L BA 8 (perilesional) during all three overt naming fMRI scans post-TMS. He still had a moderate naming deficit post-TMS, where his scores ranged 42 to 58% correct during overt naming fMRI at 3–46 mo. post-TMS. Perhaps increased activation in L posterior MFG or L posterior MTG would have been associated with better naming.

P1 had lesion only in the lowest portion of the L sensorimotor cortex area. Although there was a trend toward increasing activation in this region over time, which continues to increase even at 46 mo. post-TMS, the change was not significant. P2 had extensive lesion in the L sensorimotor cortex mouth area, thus could not activate this region during overt speech.

These fMRI data suggest additional studies with overt naming fMRI in nonfluent aphasia patients are warranted. Activation and presence of lesion in the above-mentioned DLPFC and MTG ‘epicenters’ for picture naming should be carefully examined.

7.2. Auditory comprehension post-TMS

P2 improved on auditory comprehension post-TMS, but P1 did not. For P2 pre-TMS, his mean auditory comprehension score for Commands was 8.67, and post-TMS, 11/15. Pre-TMS, his mean score for Complex Ideational Material was 2.33 and this improved to 4/12, at 6 mo. post-TMS. Although some improvements were made in auditory comprehension, a moderate-severe auditory comprehension deficit was still present post-TMS (overall, 51.7 percentile). Why P2 improved on auditory comprehen-
sion post-TMS is unknown. Improvement in auditory comprehension lasting out to 6 or 8 months post-TMS has not been an area where significant change was noted in our previous TMS studies with nonfluent aphasia patients (Naeser et al., 2005a, 2005b). Our fMRI scans only examined overt speech in the present study (not auditory comprehension), therefore no fMRI data are available for auditory comprehension, pre- and post-TMS.

7.3. Revision of TMS entry criteria

We have studied three other severe, nonfluent aphasia patients with one-word phrase length, who did not improve post-TMS (data not published, personal observation). We have observed that if, on pre-TMS language testing across three sessions, a patient did not have a mean of at least three pictures named correctly (on the first 20 pictures) of the BNT, then there was no improvement in naming, post-TMS. Overt naming fMRI scans are not available for these other cases.

We have now developed a minimum criterion for Entry into the TMS study – i.e., the patient must have a mean score of at least three pictures named correctly (on the first 20-items of the BNT) as tested across three test sessions pre-TMS. P2 would not have met this minimum criterion for Entry, as his mean BNT score across three testing sessions pre-TMS was only 1.67 (SD = 1.15, range 1–3). We have entered into the TMS protocol, one severe nonfluent aphasia patient (one-word phrase length) who was a good responder. She named four pictures on the BNT pre-TMS; seven pictures, 2 mo. post-TMS; and 12 pictures, 8 mo. post-TMS. She had primarily a subcortical lesion, and no lesion was present in the DLPFC or the posterior MTG areas (Naeser et al., 2005a).

7.4. Limitations

The application of the findings in the present study to a more general population of nonfluent aphasia patients may be limited by the following: First, there were only two patients examined with fMRI. Second, P1 entered at 10 years poststroke, whereas P2 entered at 2 years poststroke. The effect of time poststroke at entry, and potential for increased recovery before entry into the TMS study is a factor that could not be controlled for. Third, the long-term effect of the hand-held, augmentative speech device used on a daily basis by P2 (starting about 4 mo. post-TMS) on the language testing and on the fMRI scan performed at 6 mo. post-TMS, is unknown. Patients had been requested not to have individualized speech therapy intervention during the first year of participation in the study. Additionally, for P1, who showed a significant increase in verb production during narrative speech after 2 mo. of Constraint-Induced Aphasia Treatment (CIAT), the effect of CIAT (Goral & Kempler, 2008) on the fMRI activation between 16 and 46 mo. post-TMS is unknown. However, at 16 mo. post-TMS this patient had already shown a shift to his left hemisphere, which continued at 46 mo. post-TMS.

Although physiologically, TMS may have a modulating effect on the bilateral neural network for language, the TMS treatment alone, the change in performance level, or both could have influenced the observed changes in activation patterns for P1.

Future studies may want to include the use of an event-related design, which would allow analysis of responses in greater depth, particularly examination of activation patterns for correct versus incorrect responses or responses within specific categories. Recent studies have demonstrated the use of overt naming fMRI paradigms in longitudinal studies in normal controls (Meltzer et al., 2009). However, the use of an event-related de-
sign, is particularly problematic due to the multiple hesitations and false-starts during overt speech in aphasia patients. Sensitivity is also an issue, particularly with more severe nonfluent aphasia patients, who may only correctly name fewer than 3 or 4 items.

8. Summary

Suppression of R PTr with rTMS in the good responder may have promoted inhibition there, permitting better modulation of regions within the bilateral premotor, sensorimotor and temporoparietal network important for naming (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Gold & Buckner, 2002; Price et al., 2001). The role of the L SMA in conjunction with this shift was associated with sustained, improved naming up to almost 4 years post-TMS in P1. These results for the good responder are compatible with other functional imaging studies where activation of remaining LH language regions were associated with better recovery (Heiss et al., 1999; Heiss & Thiel, 2006; Perani et al., 2003; Warburton et al., 1999) and with studies that show new LH activation after speech therapy is associated with language improvement (Cornelissen et al., 2003; Leger et al., 2002; Meinezer et al., 2008; Small et al., 1998).
