Combining Functional Neuroimaging with Off-line Brain Stimulation: Modulation of Task-related Activity in Language Areas

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Abstract

■ Repetitive TMS (rTMS) provides a noninvasive tool for modulating neural activity in the human brain. In healthy participants, rTMS applied over the language-related areas in the left hemisphere, including the left posterior temporal area of Wernicke (LTMP) and inferior frontal area of Broca, have been shown to affect performance on word recognition tasks. To investigate the neural substrate of these behavioral effects, off-line rTMS was combined with fMRI acquired during the performance of a word recognition task. Twenty right-handed healthy men underwent fMRI scans before and after a session of 10-Hz rTMS applied outside the magnetic resonance scanner. Functional magnetic resonance images were acquired during the performance of a word recognition task that used English or foreign-language words. rTMS was applied over the LTMP in one group of 10 participants (LTMP group), whereas the homologue region in the right hemisphere was stimulated in another group of 10 participants (RTMP group). Changes in task-related fMRI response (English minus foreign languages) and task performances (response time and accuracy) were measured in both groups and compared between pre-rTMS and post-rTMS. Our results showed that rTMS increased task-related fMRI response in the homologue areas contralateral to the stimulated sites. We also found an effect of rTMS on response time for the LTMP group only. These findings provide insights into changes in neural activity in cortical regions connected to the stimulated site and are consistent with a hypothesis raised in a previous review about the role of the homologue areas in the contralateral hemisphere for preserving behavior after neural interference. ■

INTRODUCTION

TMS provides a noninvasive method for inferring causality in neural connectivity by employing a "perturb and measure" approach (Paus, 1999, 2005; Pascual-Leone, Bartres-Faz, & Keenan, 1999). Repetitive TMS (rTMS) applied in healthy participants has been used to examine functional organization of the language-related areas. For instance, rTMS applied over the posterior temporal area of Wernicke (LTMP) has been shown to improve performance (i.e., decrease response time [RT]) during an auditory task of word recognition (Andoh et al., 2006) and also during a picture-naming task (Mottaghy et al., 1999; Töpper, Mottaghy, Brugmann, Noth, & Huber, 1998). On the other hand, rTMS applied over the left inferior frontal gyrus (IFG) impaired (i.e., increased RT) semantic detection of simultaneously presented words (Gough, Nobre, & Devlin, 2005). Several researchers have hypothesized that these changes in performance may be related to the modified activity of the corticocortical connection between the stimulated area and the remote areas (Andoh et al., 2006; Gough et al., 2005). Previous studies combined PET with rTMS and showed changes in brain activity after rTMS not only under the coil but also in remote brain areas (reviewed in Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Paus, 2008).

Recent rTMS studies provided experimental support for the hypothesis that some brain functions operate in a state of interhemispheric compensation, recruiting especially homologous regions in the contralateral hemisphere to support functional recovery after a virtual brain lesion (O'Shea, Johansen-Berg, Trief, Gobel, & Rushworth, 2007). For example, Thiel, Schumacher, et al. (2006) demonstrated a rightward shift of activity in language networks measured as language-associated changes in CBF during rTMS interference. Specifically, these authors reported a CBF decrease in the left IFG (LIFG) and a CBF increase in the homologue contralateral (right) IFG when applying 4-Hz rTMS over the LIFG during a verb generation task. Although neuroimaging studies revealed local and distant changes in brain activity induced by TMS, no imaging data are available regarding TMS effects over the LTMP area, a key node of the language-related network.

We hypothesized that rTMS applied over the LTMP area will induce change in task-related fMRI response locally and also distally, namely, in the homologue area in the contralateral hemisphere (RTMP). Similarly, we expected that rTMS applied over the RTMP area would induce change in task-related fMRI response in the contralateral hemisphere (LTMP). Regarding behavioral performance,

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namely, RT and accuracy, we based our hypothesis on previous studies by Andoh et al. (2006, 2007), which showed that rTMS decreased RT in a similar word recognition task. We expected 10-Hz rTMS applied over the LTMP area to decrease RT to English language stimuli. No change in performance was expected following rTMS applied over the RTMP area.

METHODS

Participants

Twenty healthy male volunteers (mean age ± *SD* = 21.8 ± 4.3 years) gave written informed consent for the study, which was approved by the Nottingham University Medical School Ethics Committee. They were all native English speakers unfamiliar with the foreign languages used in this study, namely, Polish, Korean, and Japanese.

All participants were right-handed as determined using a modified version of the Crovitz and Zener (1962) handedness questionnaire (mean score ± *SD* = 27.2 ± 6.1). This 18-item inventory has scores ranging from 18 to 90 for extreme right-handers and extreme left-handers, respectively. Participants were divided into two groups matched according to age, education level, and handedness (two-sample t test: $t = 0.45$, $p = .66$; $t = 0.35$, $p = .73$; and $t = 0.25$, $p = .81$, respectively), with no history of neurological disease, head injury, or hearing impairment. Written informed consent was obtained, and volunteers were compensated for participation. TMS sessions were performed according to the published safety guidelines (Wassermann, 1996).

Task Description

The language paradigm used here was modified from Pallier et al. (2003, see Figure 1A). The participants listened to sentences in their native language (English) and in languages unknown to them (Korean, Polish, and Japanese) and were asked to perform the following task. After each 3-sec sentence and a 0.5-sec delay, a word of 0.5 sec was played and the participants had to press one of two response buttons to indicate whether the word had appeared in the previous sentence. "Present" was indicated by pressing the right button with the right thumb, and "Not present" was indicated by pressing the left button with the left thumb. The intertrial interval was 8 sec. Each run of the language task consisted of a total of 120 trials: 40 sentences in English, 40 sentences in foreign languages (Korean, Japanese, and Polish), and 40 periods of silence. Languages and sides of response were presented in a different randomized order for each participant. In total, participants had four different runs of the language task, that is, the practice session, the fMRI localizer session, the fMRI pre-rTMS session, and the post-rTMS session. A PC running E-Prime software (Psychology Software Tools, Pittsburgh, PA) played the auditory stimuli and recorded the responses.

Magnetic Resonance Imaging

Anatomical MRI Acquisition

A high-resolution T1-weighted three-dimensional image was acquired for each participant on a Phillips 1.5-T scanner using a gradient-echo sequence (repetition time/echo time = 9.9/4.6, 170 slices, 1-mm isotropic resolution, matrix = 256 × 251).

Functional MRI Acquisition

Each volunteer participated in two sessions (i.e., fMRI localizer and fMRI/rTMS) on two separate days. In the first session (fMRI localizer), participants first completed a practice run (120 trials) of the language task outside of the scanner and then an fMRI scan during another run of the

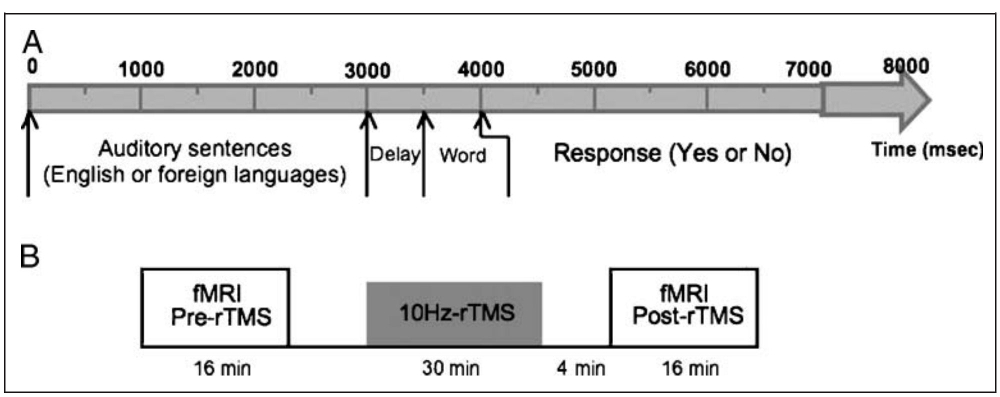

Figure 1. (A) Word recognition task. Participants pressed right or left thumb response buttons depending on whether a 0.5-sec entire word was present in the sentence just heard. (B) TMS/fMRI design. Participants underwent two fMRI sessions, one of which was preceded by 10-Hz rTMS (15 ten-pulse trains of 1 sec, 10-sec intertrain interval). The post-rTMS fMRI session started less than 4 min after the end of the 10-Hz rTMS trains. A total of 450 TMS pulses were delivered over a period of 30 min preceding the start of fMRI acquisition (Strafella & Paus, 2001).

language task (see task description above). In a pilot study, we confirmed that two runs of the language task (i.e., 2 × 120 trials) were sufficient to minimize further improvements in the RT (unpublished results).

In the second session (fMRI/rTMS), participants underwent two fMRI sessions, one of which was preceded by rTMS. The post-rTMS fMRI session started less than 4 min after rTMS (see below for details). The site of the stimulation (i.e., LTMP, RTMP) was counterbalanced across participants.

A gradient-echo EPI pulse sequence was acquired in an ascending order (repetition time/echo time = 3000/60, 4 mm isotropic, 30 slices, and a 64 × 64 matrix size). Auditory events were synchronized using E-Prime software with event-related functional magnetic resonance image volume acquisitions.

Functional MRI Data Analyses

For preprocessing and statistical analysis of the fMRI data, we used the Statistical Parametric Mapping software package, version 2 (MATLAB 7.3; MathWorks, Natick, MA). All functional images were realigned to the first image, coregistered with the T1-weighted structural image, spatially normalized (voxel size = 2 mm^3) to the Montreal Neurological Institute (MNI-305 space), and spatially smoothed using a 5-mm (FWHM) isotropic, three-dimensional Gaussian filter. SPMs of group analysis were generated using the contrast files of the first-level analysis to identify localization, cluster level, MNI-305 coordinates, and size of fMRI response. Individual and group results were examined at the voxelwise threshold of $p < .001$ uncorrected for multiple comparisons.

The BOLD response to the onset of each sentence was convolved with the hemodynamic response function and its temporal derivative. Head motion was modeled by six regressors of no interest (the three rigid-body translations and the three rotations determined from initial registration) that were orthogonalized to the design. After careful inspection of the imaging data, the motion-related artifacts were less than 2 mm in any direction; consequently, all the data sets were used for the statistical analyses. We calculated statistic parametric maps (first-level analysis) for each individual and for each session (fMRI localizer and fMRI pre- and post-rTMS) using t contrasts (t test) of SPM contrast manager.

Localizer Session: Determination of the TMS Sites from Magnetic Resonance Images

Images of parameter estimates for each contrast of interest were created for each participant for (1) the determination of the areas where English elicited stronger task-related response than foreign-language words and (2) the localization of the left motor cortex using the right and left thumb motor responses to facilitate the determination of the motor threshold (MT) in the rTMS session.

These t maps were then transformed in the subject's native MRI space using the reversed native-to-MNI transformation matrix.

The LTMP target was defined in a two-step procedure: First, an a priori temporal ROI was identified using a similar word recognition task created from a separate group of 14 subjects (Andoh et al., 2007). The location of the peak posterior-temporal response in this previous study was reported in Talairach space (Talairach & Tournoux, 1988) at $x = -47 \pm 5$, $y = -47 \pm 11$, and $z = 3 \pm 10$ and included parts of the middle temporal gyrus (MTG) and the superior temporal gyrus (STG) (Andoh et al., 2007). To define this response in the MNI-305 space, these coordinates were converted using an algorithm available at http://brainmap.org/icbm2tal/index.html. This location was then used to define a spherical ROI with a 5-mm radius (a priori LTMP ROI) centered at $x = -50$, $y = -48$, and $z = 4$, and all subsequent analyses were conducted in the MNI standard space. Second, for each subject, the LTMP target was defined by the response focus nearest to the a priori LTMP ROI. For the RTMP group, the RTMP target was defined by the site opposite to the LTMP target.

Maximal intersubject variability for the location of the LTMP target was calculated across participants for each group using the Euclidean distance.

Combined fMRI/TMS Session

Participants performed two fMRI sessions, one before and another one after rTMS. The post-rTMS fMRI session started less than 4 min after the end of the 10-Hz rTMS trains (Figure 1B). To evaluate differences of pre- and post-rTMS sessions, we performed a random-effect analysis using Student's paired t test in RTMP and LTMP groups separately. To clarify the nature of the task-related changes in fMRI response induced by rTMS, a series of spherical ROIs of 5-mm radius were identified from the paired t test analysis of each group. For both groups, we created four bilateral ROIs: (1) the LTMP ROI defined by the response focus nearest to the a priori LTMP ROI (i.e., at $x = -50$, $y = -48$, $z = 4$); (2) the RTMP ROI defined by the response focus nearest to the opposite site of the a priori LTMP ROI (i.e., at $x = 50$, $y = -48$, $z = 4$); (3) the LIFG ROI (including pars opercularis, pars triangularis, and pars orbitalis) defined functionally and anatomically, using anatomical borders according to the following guidelines: delimited ventrally by the lateral orbital sulcus and dorsally by the inferior segment of the precentral sulcus (see Devlin, Matthews, & Rushworth, 2003); and (4) the right IFG (RIFG) ROI defined by the opposite site of the LIFG ROI. Mean values of percent BOLD signal change (%BSC) in these clusters were calculated for each condition, Group (LTMP, RTMP) and fMRI Session (pre-rTMS, post-rTMS), and contrasted across conditions using repeated measures ANOVA.

In addition, we wished to identify brain areas of the word recognition network in which the correlation with the LTMP ROI response changed as a function of both task and TMS. For each group, we carried out a regression analysis between the task-related fMRI response in the LTMP ROI and fMRI response in other brain regions. The time course across all voxels within the LTMP ROI was found and correlated with the English minus foreign-language words contrast, which identified voxels showing a greater correlation with the fMRI response in LTMP ROI during the English than during the foreign-language words. A higher level random-effects analysis identified voxels captured by this contrast in which task-related fMRI response differed in the post- minus pre-rTMS session.

Finally, behavioral data (mean RT for correct trials and accuracy) for English and foreign-language words stimuli were also analyzed to test for a difference in the effect of rTMS before and after rTMS.

Transcranial Magnetic Stimulation

The TMS experiment took place a few days after the fMRI localizer. A real-time optically tracked frameless stereotaxic system (Brainsight Frameless, Rogue Research Inc., Montreal, QC, Canada) was used to guide the coil over the subject's scalp. Focal TMS was delivered using a Magstim Rapid2 stimulator (Magstim Ltd., Whitland, Carmarthenshire, Wales, UK) equipped with a 70-mm figure-of-eight-shaped coil. Every stimulation was carried out throughout the entire experiment with the handle pointing backward and approximately 45° lateral from the midline. Three blocks of rTMS were delivered, each block separated by a 10-min interval. Each block consisted of 15 trains of 10-pulse of 1-sec duration (i.e., 10 Hz) with an intertrain interval of 10 sec. Thus, a total of 450 stimuli were delivered over a period of 30 min preceding the start of fMRI acquisition; similar protocol has been used in our previous studies (Barrett, Della-Maggiore, Chouinard, & Paus, 2004; Strafella, Paus, Barrett, & Dagher, 2001). The stimulus intensities, which were expressed as a percentage of the maximum stimulator output, were set at the resting MT, namely, the lowest stimulus intensity able to elicit a motor-evoked potential MEP >50 μV in the relaxed abductor pollicis brevis (APB) in 5 of 10 consecutive trials delivered over the left primary motor cortex at intervals >5 sec (Rothwell et al., 1999).

Statistical Analysis of Behavioral Data

Statistical analyses were performed using JMP software (SAS Institute, Acton, MA, USA). The behavioral variables (RT and accuracy) were analyzed using repeated measures ANOVA with three within-subject factors: Group (LTMP, RTMP), fMRI Session (pre-rTMS, post-rTMS), and Language (English, foreign-language words). Paired t tests were used for post hoc analysis.

RESULTS

MTs ranged between 48% and 75% of maximum stimulator output for the LTMP group (mean ± *SD* = 63 ± 9%) and between 45% and 85% for the RTMP group (mean ± *SD* = 66 ± 11%); this group difference was not significant ($t = -0.6$, $p > .5$, $df = 17$).

Behavioral Results

Before rTMS, the percentage of correct responses for the English stimuli ranged from 72.5% to 100.0% (mean ± *SEM* = 88.8 ± 2.9%) for the LTMP group and from 52.5% to 100% for the RTMP group (mean ± *SEM* = 88.5 ± 4.6%). The percentage of correct responses for the foreign languages ranged from 47.5% to 85.0% (mean ± *SEM* = 65.5 ± 3.5%) for the LTMP group and from 50% to 90% for the RTMP group (mean ± *SEM* = 69.5 ± 3.4%) (see Table 1A). Accuracy was not significantly modified by rTMS, either in the LTMP group (paired t tests, $t = 1.92$, $p = .07$, $df = 19$) or in the RTMP group (paired t tests, $t = -0.44$, $p = .66$, $df = 19$).

Before rTMS, the average RTs for the correct responses to the English stimuli ranged from 567 to 1054 msec (mean ± *SEM* = 874 ± 50 msec) for the LTMP group and from 675 to 969 msec (mean ± *SEM* = 838 ± 32 msec) for the RTMP group. The average RTs for the correct responses to the foreign-language stimuli ranged from 732 to 1214 msec (mean ± *SEM* = 1040 ± 55 msec) and from 944 to 1272 msec (mean ± *SEM* = 1096 ± 31 msec) for the RTMP group (see Table 1B). A significant main effect of language was detected for RT, $F(1, 36) = 25.05$, $p < .01$, indicating that RT for foreign-language words was slower than RT for English words. There was a significant interaction between Group and fMRI session, $F(1, 36) = 4.9$, $p = .03$ (see Figure 2). Post hoc analyses showed that, for the LTMP group, the RT decreased after rTMS (paired t test: $t > -2.13$, $p = .04$, $df = 19$). For the RTMP group, no change in RT has been detected after rTMS (paired t test: $t = 1.35$, $p = .2$, $df = 19$). There was no interaction between Group, fMRI Session, and Language, $F(1, 36) = 0.04$, $p < .85$.

Table 1. Behavioral Data (Accuracy and RT) Pre- and Post-rTMS for the LTMP and RTMP Groups

	English Words		*Foreign-language Words*	
	Pre-rTMS	*Post-rTMS*	*Pre-rTMS*	*Post-rTMS*
A. Mean Accuracy ± SEM (%)				
LTMP group	88.8 ± 2.9	93.0 ± 1.8	65.5 ± 3.5	72.0 ± 3.7
RTMP group	88.5 ± 4.6	85.5 ± 2.6	69.5 ± 3.4	69.5 ± 2.7
B. Mean RT ± SEM (msec)				
LTMP group	874 ± 50	844 ± 50	1040 ± 55	1025 ± 54
RTMP group	838 ± 32	858 ± 36	1096 ± 31	1123 ± 43

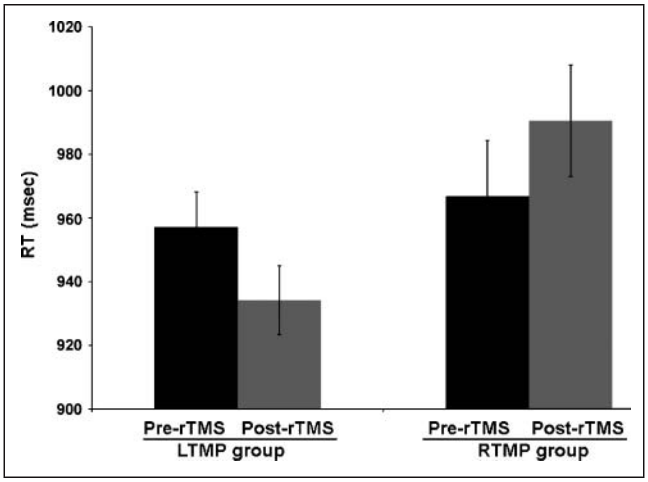

Figure 2. Effect of 10-Hz rTMS on RTs for each group. (Left) The LTMP group showed a significant decrease of RTs after rTMS (paired t test: $t > -2.13$, $p = .04$, $df = 19$). (Right) No significant change of RTs after rTMS has been found in the RTMP group (paired t test: $t = 1.35$, $p = .2$, $df = 19$). Error bars = 1 *SEM*.

Functional Imaging Results: Localizer Session

The SPM resulting from the English minus foreign-language contrast detected task-related fMRI response in the a priori LTMP ROI for all participants (Figure 3A, Table 2). The MNI coordinates for the LTMP "peaks," which served as TMS targets in this group, were averaged across subjects (mean ± SD = −59.0 ± 6.1, −41.2 ± 5.5, 5.0 ± 3.3; $Z > 4.7$; extent = 9502 ± 12714 mm^3). Maximal Euclidean distance of the LTMP peaks across participants was 21.9 mm (Figure 3B, left).

For the RTMP group, the MNI coordinates for the LTMP "peaks" were averaged across subjects (mean ± SD = −58.0 ± 7.6, −47.0 ± 8.0, 5.4 ± 2.5; $Z > 4.1$; extent = 9857 ± 9817 mm^3). For the rTMS session, these coordinates were flipped in the x direction to indicate the RTMP target for TMS in each participant (Table 2). Maximal Euclidean distance of the RTMP target across participants was 19.3 mm (Figure 3B, right).

Functional Imaging Results Pre- and Post-rTMS Sessions: Task-related fMRI Response

Pre-rTMS fMRI in both groups showed similar BOLD signal changes in the LTMP ROI, LIFG (pars triangularis), left STG

Figure 3. Cortical stimulation sites. (A) Individual SPM for the fMRI subtraction "English minus Foreign-language words." The stimulation site (peak voxel at −52, −54, 4, $t = 9.48$) was defined by the response focus nearest to an a priori defined region form previous work of Andoh et al. (2007) (i.e., −50, −48, 4). (B) Each circle represents the stimulation site for an individual subject at which rTMS was applied (left) over the left LTMP target ($n = 10$) or (right) over the right RTMP target ($n = 10$).

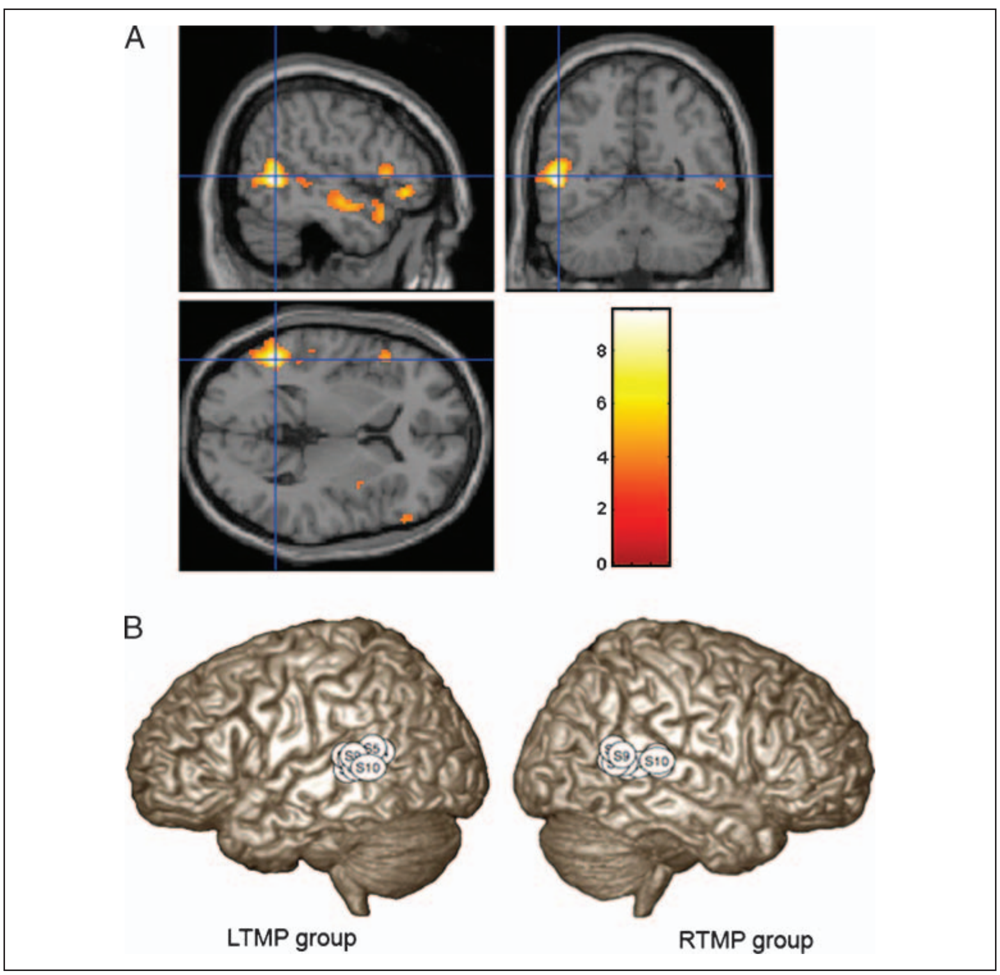

Table 2. Individual Coordinates of the LTMP Target for the English Minus Foreign Languages (Voxelwise Threshold of $p < .001$ Uncorrected)

	MNI Coordinates (mm)			*Voxel Level*		*Cluster Level*
Participants	*x*	*y*	*z*	*t*	*Z score*	*Extent (mm^3)*
LTMP Group						
S1	−62	−38	2	4.98	4.85	768
S2	−64	−38	2	4.79	4.68	528
S3	−54	−36	2	5.43	5.27	6208
S4	−68	−52	8	5.44	5.28	6664
S5	−64	−48	10	11.76	>8	44040
S6	−58	−36	8	6.64	6.36	8472
S7	−62	−38	6	5.84	5.65	2472
S8	−50	−40	2	10.96	>8	13344
S9	−50	−40	8	6.05	5.83	6216
S10	−58	−46	2	6.39	6.14	6312
RTMP Group						
S1	−56	−56	4	6.6	6.33	2432
S2	−56	−38	4	7.58	7.18	14376
S3	−64	−48	2	10.58	>8	32328
S4	−48	−44	4	5.23	5.08	2264
S5	−68	−50	4	5.76	5.57	7928
S6	−52	−54	4	9.48	>8	4456
S7	−62	−56	10	6.88	6.58	17952
S8	−62	−36	8	7.53	7.13	4256
S9	−46	−52	8	6.1	5.88	12368
S10	−66	−36	6	4.19	4.11	208

For the RTMP group, these coordinates were flipped in the *x* direction to localize the RTMP target.

and MTG, and right STG and MTG (Table 3). There was no significant group difference (p corrected $< .05$).

After rTMS, the LTMP group showed significantly enhanced task-related fMRI response in the right MTG, in the right STG, and in the left cerebellum when compared with pre-rTMS fMRI. In addition, there was a decrease in task-related fMRI response in the left MTG, in the left STG, and in the LIFG as compared with pre-rTMS fMRI (Table 4).

In contrast, the group that received rTMS over the RTMP target showed an increase (post- vs. pre-rTMS) in task-related fMRI response in the left STG, the left cingulate gyrus, the right cerebellum, and the superior and middle frontal gyri bilaterally. There was also a decrease in task-related fMRI response in the left posterior cingulate cortex and in the left precentral gyrus after rTMS (Table 5).

Repeated measures ANOVA of mean percent BOLD signal change (%BSC) was carried out with factors of ROIs (LTMP, RTMP, LIFG, RIFG), Group, and fMRI Session. There were significant Group × fMRI session interaction, $F(1, 36) = 9.5$, $p < .01$, and ROI × Group interaction, $F(1, 34) = 6.9$, $p < .01$. The three-way interaction between ROIs, Group, and fMRI Session was significant, $F(1, 34) = 5.3$, $p < .01$. Separate analyses were then carried out for each ROI. There was a significant main effect of Group for the LTMP ROI, $F(1, 18) = 26.9$, $p < .01$, confirming that, after rTMS, the %BSC in the LTMP ROI was significantly lower in the LTMP group (paired t tests: $t = -2.82$, $p = .02$, $df = 9$) and significantly higher in the RTMP group (paired t tests: $t = 4.4$, $p < .01$, $df = 9$) (see Figure 4A and B). In addition, after rTMS, the LTMP group showed a significant increase in task-related fMRI response in the RTMP ROI (paired t tests: $t = -3.2$,

Table 3. fMRI Response before rTMS for the LTMP and RTMP Groups

	MNI Coordinates			*Voxel Level*		
Brain Area	*x*	*y*	*z*	*t*	*Z score*	*Cluster (mm^3)*
LTMP Group						
Left MTG	−56	−4	−10	10.6	4.7	7032
Left MTG	−60	−40	4	10.6	4.7	
Left MTG	−52	−34	2	8.5	4.4	
Left supramarginal gyrus	−58	−48	20	7.5	4.1	
Left STG	−50	−56	18	6.4	3.8	
LIFG	−58	24	4	11.1	4.8	944
Right STG	46	−38	2	10.1	4.6	696
Right MTG	56	8	−18	5.9	3.7	
Right fusiform gyrus	48	14	−24	11.2	4.8	864
RTMP Group						
Left STG	−56	10	−18	12.6	5.0	2800
Left STG	−64	−46	8	7.0	4.0	584
Left STG	−62	−34	8	6.6	3.9	168
LIFG	−42	34	−14	5.1	3.4	64
Right STG	50	−22	−6	5.8	3.7	344
Right cingulate gyrus	8	32	34	10.6	4.7	176

Table 4. rTMS-induced Changes in the LTMP Group

	MNI Coordinates			*Voxel Level*		
Brain Area	*x*	*y*	*z*	*t*	*Z score*	*Cluster (mm^3)*
Post- Minus Pre-rTMS						
Right MTG	42	−56	8	5.47	3.54	32
Right STG	46	−22	0	4.88	3.33	8
Left cerebellum (anterior lobe)	−16	−42	−28	6.33	3.82	40
Pre- Minus Post-rTMS						
Left superior parietal lobule	−30	−48	66	7.04	4.01	80
Left temporal lobe, fusiform gyrus	−44	−46	−10	5.68	3.61	56
Left STG	−52	−40	20	5.64	3.6	64
Left MTG	−44	−12	−10	2.39	3.51	48
LIFG, pars orbitalis	−34	16	−14	6.85	3.96	104
Right parahippocampal gyrus	30	−22	−16	5.33	3.49	120

p = .01, df = 9) and a significant decrease in task-related fMRI response in the LIFG ROI (paired t tests: $t = -4.83$, $p < .01$, df = 9), but no changes were found in the RIFG ROI (paired t tests: $t = -0.49$, $p = .64$, df = 9). In the RTMP group, the difference in the %BSC between pre- and post-rTMS was not significant for any ROI other than the LTMP as indicated above (RIFG ROI: paired t tests $t = 1.76$, $p = .1$, df = 9; RTMP ROI: paired t tests $t = -0.8$, $p = .4$, df = 9; and LIFG ROI: paired t tests $t = -1.2$, $p = .2$, df = 9).

Table 5. rTMS-induced Changes in the RTMP Group

	MNI Coordinates			*Voxel Level*		
Brain Area	*x*	*y*	*z*	*t*	*Z score*	*Cluster (mm^3)*
Post- Minus Pre-rTMS						
Left cingulate gyrus	0	26	30	7.88	4.21	120
Left middle frontal gyrus	−34	36	23	7.1	4.03	48
Left superior frontal gyrus	−12	28	48	6.25	3.79	72
Left STG	−40	−50	22	6.92	3.98	96
Left transverse temporal gyrus	−52	−23	10	6.1	3.75	248
Left posterior cingulate	−8	−54	19	6.88	3.97	104
Right cerebellum	10	−52	−6	6.71	3.92	256
Right medial frontal gyrus	10	58	5	8.23	4.29	176
Right superior frontal gyrus	14	4	57	7.12	4.03	80
Pre- Minus Post-rTMS						
Right middle frontal gyrus	54	38	14	5.15	3.43	8
Left posterior cingulate	−8	14	16	5.61	3.59	152
Left precentral gyrus	−12	−8	28	4.98	3.37	56

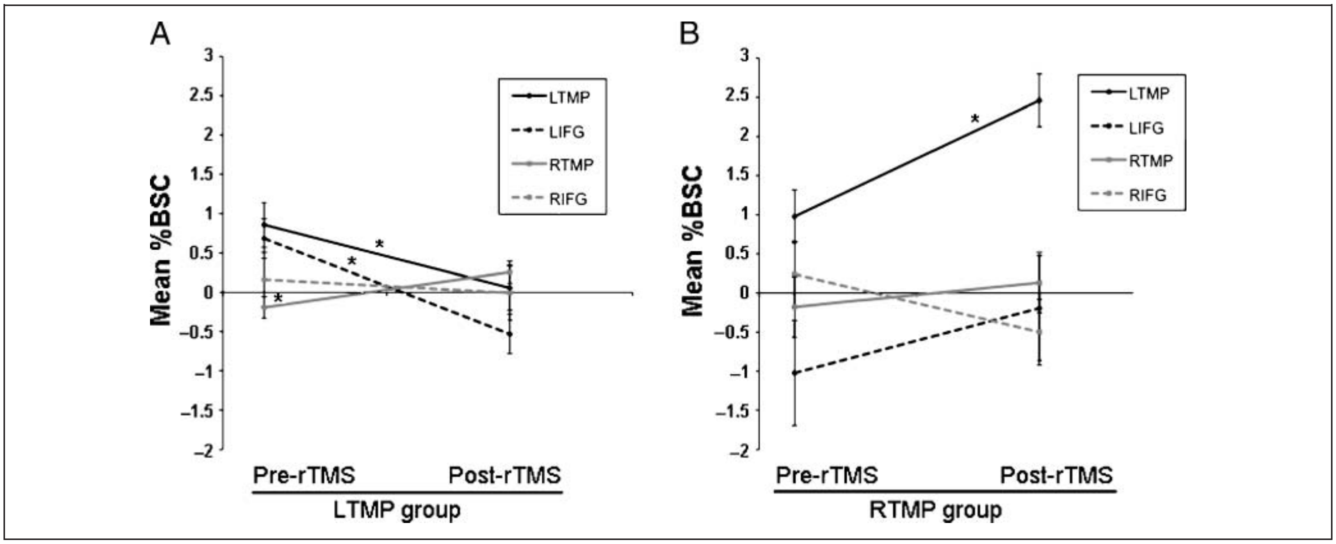

Figure 4. The graph shows mean percent BOLD signal change (%BSC) values for the contrast English minus foreign languages pre- and post-rTMS sessions. (A) For the LTMP group, rTMS induced significant increase in %BSC in the right RTMP ROI, area contralateral to the stimulation site (paired *t* tests: $t = -3.2$, $p = .01$, $df = 9$), and a significant decrease in %BSC in the LTMP ROI (paired *t* tests: $t = -2.82$, $p < .01$, $df = 9$) and in the LIFG ROI (paired *t* tests: $t = -4.83$, $p < .01$, $df = 9$). No significant change in the %BSC was found in the RIFG ROI after rTMS (paired *t* tests: $t = 0.49$, $p = .64$, $df = 9$). (B) For the RTMP group, rTMS induced significant increase in %BSC in the LTMP ROI (paired *t* tests: $t = 4.4$, $p < .01$, $df = 9$), area contralateral to the stimulation site. The decrease in %BSC in the RIFG ROI after rTMS did not reach significance (paired *t* tests: $t = -1.76$, $p = .1$, $df = 9$). No change in %BSC was detected between pre- and post-rTMS in the RTMP ROI (paired *t* tests: $t = -0.8$, $p = .4$, $df = 9$) or in the LIFG ROI: (paired *t* tests: $t = -1.2$, $p = .2$, $df = 9$). Error bars = 1 *SEM*.

Functional Imaging Results Pre- and Post-rTMS Sessions: Regression Analysis between the TMS-induced Change in Task-related fMRI Response in LTMP ROI and the Change in Task-related Response in Other Brain Regions

In the LTMP group, after rTMS, we found that the TMS-induced change in task-related fMRI response in LTMP ROI correlated positively with task-related response within the right STG and the left middle and superior frontal gyri (see Figure 5A, Table 6). In addition, after rTMS, the TMS-induced change in task-related response in LTMP ROI correlated negatively with the response within the right medial and middle frontal gyri (Table 6).

In the RTMP group, after rTMS, the regression analysis showed that the task-related fMRI response in the LTMP ROI correlated positively with the response in the left frontal gyrus, including the superior, the medial, and the middle frontal gyri and the IFG in the pars opercularis (see Figure 5B, Table 7). In addition, after rTMS, the regression analysis showed that the fMRI response in the LTMP ROI correlated negatively with the response in the left cerebellum and in the right ACC (Table 7).

DISCUSSION

We have shown that rTMS applied over either the LTMP or the RTMP targets increased the task-related fMRI response in the areas contralateral to the stimulated sites. For the LTMP group, rTMS increased the task-related fMRI response in the right temporal cortex, including the right MTG and the right STG. For the RTMP group, rTMS increased the task-related fMRI response in the left temporal cortex, including the left STG and the left transverse temporal gyrus.

Similar changes in activity in language-related network were found by Thiel, Schumacher, et al. (2006), who reported a CBF decrease in the stimulated LIFG and a CBF increase in the homologous (contralateral) RIFG during a verb generation task. The authors explained their findings by a reduction of transcallosal inhibitory activity of the language-dominant left hemisphere caused by rTMS interference.

More recently, a mechanism of rTMS effect on brain activity has been highlighted supporting the hypothesis that some brain functions operate in a state of interhemispheric compensation after a virtual brain lesion, that is, a form of adaptive plasticity in the nondominant hemisphere for functional recovery (O'Shea et al., 2007; Thiel, Habedank, et al., 2006). These plastic-adapting changes of the intact hemisphere could occur rapidly (>4 min after the end of TMS) and be specific to functions that are normally mediated by the perturbed area. O'Shea et al. (2007) directly demonstrated the interhemispheric compensation by testing the hypothesis that if the pattern of reorganization causes recovered behavior, then recovery performance should breakdown when activity is disrupted in the compensatory hemisphere. The authors applied 1-Hz rTMS over the left dorsal premotor cortex (PMd) and showed a compensatory increase in fMRI response in the right PMd and the connected medial premotor areas. Subsequent TMS of the "reorganized" right PMd disrupted performance, confirming that the pattern of functional reorganization of

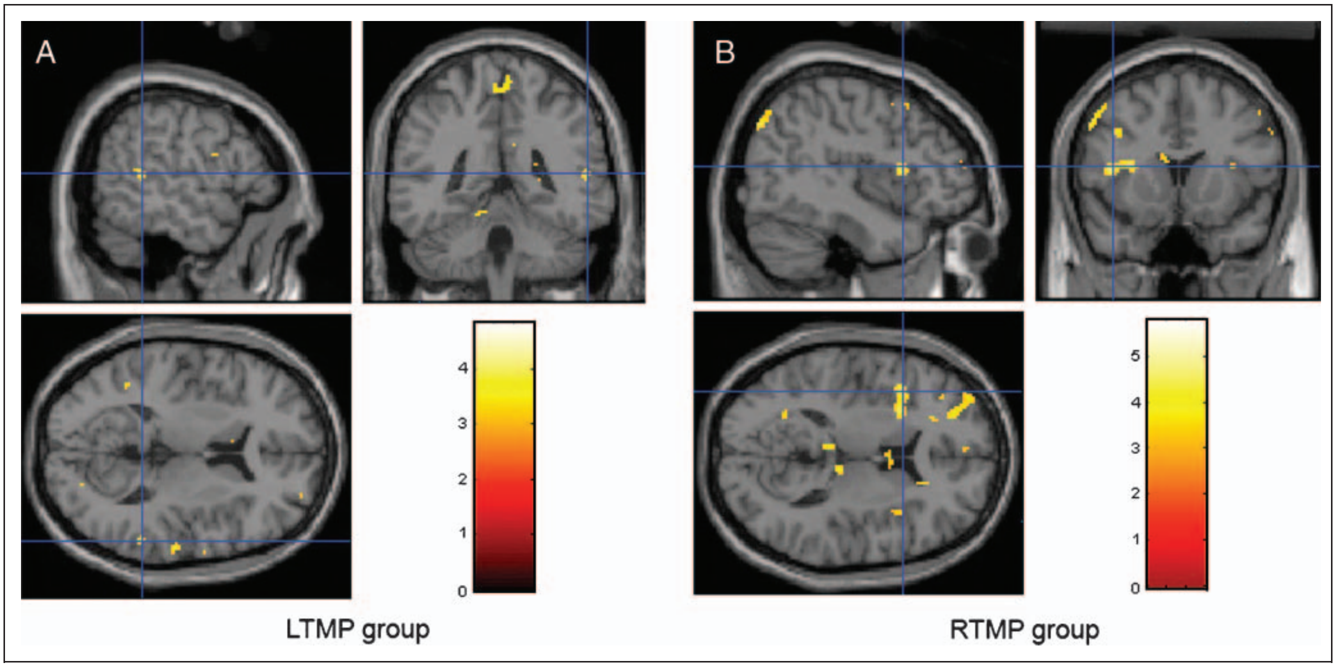

Figure 5. A random effects analysis identifying voxels captured by the contrast English minus foreign showing a regression analysis between the TMS-induced activity change in task-related fMRI response in LTMP ROI and the change in task-related fMRI response in other brain regions after rTMS. (A) LTMP group, after rTMS, positive correlation was found between the TMS-induced change in task-related fMRI response in LTMP ROI and task-related response within the right STG (peak voxel at 54, −42, 10; t = 4.08, extent = 160 mm^3). (B) RTMP group, after rTMS, positive correlation was found between the task-related fMRI response in LTMP ROI and response in the LIFG, pars opercularis of Broca's area (peak voxel at −44, 14, 12; t = 4.75, extent = 1032 mm^3).

Table 6. Regression Analysis between the TMS-induced Activity Change in LTMP ROI and fMRI Response in Other Brain Regions in the LTMP Group

	MNI Coordinates			*Voxel Level*		
Brain Area	*x*	*y*	*z*	*t*	*Z score*	*Cluster (mm^3)*
Post- Minus Pre-rTMS						
Left superior frontal gyrus	−4	10	68	4.85	4.84	376
Left superior frontal gyrus	−14	60	32	3.87	3.86	80
Left middle frontal gyrus	−28	14	66	4.33	4.33	128
Right STG	54	−42	10	4.08	4.08	160
Right transverse temporal gyrus	58	−20	10	3.89	3.89	112
Right cerebellum	14	60	−6	3.88	3.88	152
Right parahippocampal gyrus	24	−48	4	3.72	3.72	120
Pre- Minus Post-rTMS						
Right medial frontal gyrus	18	64	4	4.25	4.24	208
Right middle frontal gyrus	28	20	54	4.16	4.16	136
Left cerebellum	−24	−32	−26	4.91	4.9	408
Left parahippocampal gyrus	−30	−20	−18	4.04	4.04	160
Left precentral gyrus	−56	0	10	3.98	3.98	112

Table 7. Regression Analysis between the Task-related fMRI Response in the LTMP ROI and fMRI Response in Other Brain Regions in the RTMP Group

Brain Area	*MNI Coordinates* *x*	*y*	*z*	*Voxel Level* *t*	*Z score*	*Cluster* (mm^3)
Post- Minus Pre-rTMS						
Left medial frontal gyrus	−4	54	46	5.79	5.78	3224
Left superior frontal gyrus	−18	68	22	5.37	5.36	488
Left middle frontal gyrus	−48	6	52	5.1	5.1	1024
LIFG	−44	14	12	4.75	4.75	1032
Left posterior cingulate	−30	−62	10	4.62	4.61	232
Right cerebellum	4	−50	−38	5.33	5.32	784
Right superior frontal gyrus	16	56	40	5.29	5.28	1512
Pre- Minus Post-rTMS						
Left supramarginal gyrus	−52	−50	17	5.45	5.44	1336
Left STG	−48	−33	17	4.8	4.79	10568
Left STG	−56	−61	16	3.28	3.28	1336
Left cerebellum	−42	−59	−25	5.28	5.27	664
Right anterior cingulate	6	26	12	5.36	5.36	360
Right MTG	56	−35	−2	4.48	4.77	4040

the right PMd made a causal contribution in preserving behavior after neuronal interference.

In the language domain, our findings are in accordance with a hypothesis raised by Andoh and Martinot (2008) in a review of the rTMS use as a therapeutic tool in disorders related to dysfunctions of language processing (e.g., schizophrenia patients with auditory hallucinations, patients with tinnitus). We hypothesized that therapeutic effects of rTMS applied over the "dysfunctional" Wernicke's area might induce a local inhibition of the targeted area, which in turn may lead to a compensatory increase in activation in the right hemispheric homologue of Wernicke's area (Andoh & Martinot, 2008).

The current findings are also consistent with recent literature on recovery of language processing after a brain lesion, which suggest compensatory functional changes in right frontal or temporal regions. Functional changes in the right frontal lobe are more likely observed after damage to the left frontal lobe (Peck et al., 2004; Rosen et al., 2000); similar findings were also observed in case of the temporo-parietal damage (Fernandez et al., 2004; Rosen et al., 2000).

One additional finding observed in the present study was that the LTMP group showed a decrease in task-related fMRI response in the LTMP ROI, the area ipsilateral to the stimulated site, which was also accompanied by a decrease in task-related fMRI response in the ipsilateral IFG (BA47). It is likely that the two regions, that is, the left posterior temporal cortex and areas in the LIFG, are connected by fibers contained in the arcuate fasciculus (Catani, Jones, & Ffytche, 2005; Parker et al., 2005). The decrease in fMRI response in the LTMP ROI, however, did not seem to correlate with the decrease in fMRI response in the LIFG ROI.

Furthermore, we observed that the decreased fMRI response observed in the stimulated region was present only in the LTMP group. It is of note that the task performance, namely, a decrease of RT after rTMS for the native language, was affected only in this group, with no such effects in the RTMP group. These findings are consistent with our previous studies where we reported similar decreases of RT for the native language with 1 Hz and also with 50 Hz bursts of rTMS (Andoh et al., 2006, 2007). It is, however, unclear whether the improvement in the RT was related to the increased fMRI response in the contralateral RTMP ROI or to the decreased fMRI response in the LTMP ROI. Considering the RT improvement for the LTMP group only, we can hypothesize that rTMS might have modified the trade-off between semantic/phonologic functions, which are implemented by the left hemisphere (Friederici, 2002), and the prosodic function (tone of voice), which relies mainly on temporo-frontal systems of the right hemisphere (Friederici & Alter, 2004). Indeed, several studies have shown that prosody is processed mainly in the right STS/inferior parietal lobule (Buchanan et al., 2000; George et al., 1996). The increased fMRI response in the right temporal gyrus observed in our study could reflect an increased sensitivity to certain features of speech and, in turn, enhanced perception of prosody signals. Mitchell, Elliott, Barry, Cruttenden, and Woodruff (2003) acquired fMRI in healthy volunteers during passive listening to speech, filtered so that it contained only prosody without discernible semantic features, and showed fMRI response in the temporal cortex that was stronger in the right than in the left hemisphere. We hypothesize that some of the observed behavioral effects could be due to right hyperresponsiveness of the temporal cortex to emotional and/or linguistic prosody. We also speculate that a very high frequency TMS (e.g., theta burst stimulation [TBS]) might induce even stronger changes in fMRI response in the right temporal cortex compared with 10-Hz rTMS and, as such, could increase the facilitatory effect for prosodic processing compared with tasks that require semantic processing as we found in a previous work comparing TBS with 1-Hz rTMS (Andoh et al., 2007).

An alternative interpretation of our findings may consider possible changes in the speed of processing during the word recognition task. We found an increased fMRI response in the bilateral STG in some subjects, which has been previously associated with short-term recognition memory (Buchsbaum & D'Esposito, 2009; for a review, see Buchsbaum & D'Esposito, 2008). The decrease in fMRI response in the LTMP ROI in the LTMP group observed in our study may reflect a change in processing time, possibly shortened for the LTMP group by processing words in the right STS only. The RTMP group did not show a local effect of TMS so the processing time during the word recognition task might have not been modified.

This is one of a few studies showing a decrease in fMRI response following high-frequency rTMS. It is generally assumed that high-frequency rTMS "excites" the neuronal population in the stimulated cortex (Pascual-Leone et al., 1998). The neurophysiological mechanisms of rTMS that modulate cortical excitability are not well understood, however. At the microscopic level, it is unknown which set of axons are initially activated by the electric field induced by TMS. At the network level, TMS effects may be excitatory of inhibitory depending on the stimulation parameters, such as intensity and frequency, but also depending on intrinsic factors, such as the functional state of the stimulated cortex (Siebner et al., 2009; for a review, see Siebner & Rothwell, 2003). In our study, the decreased fMRI response under the coil during suprathreshold TMS applied over the LTMP ROI may be related to interregional differences in cortical excitability. For example, we have shown (Paus et al., 1997, 1998) that applying TMS with the same parameters to different brain regions may yield decreases or increases of resting CBF depending on the brain region. It is further unclear whether the resting MT, which is determined as the minimum stimulator output leading to a discharge of cells in the primary motor cortex, is a good indicator of stimulation "threshold" in other cortical regions, including the LTMP. It might be that stimulating the LTMP at resting MT (as determined over the motor cortex) is, in fact, subthreshold and that such a subthreshold stimulation causes an ipsilateral decrease in resting fMRI response.

Limitations

Our findings should be interpreted with caution, however, because of the relatively subtle effects of TMS on the fMRI response and the relatively low number of participants. The low modulation of the task-related fMRI response could be due to a rather high intersubject variability in the TMS response, in the location of TMS targets and/or in the ROIs definition. Our analysis used anatomical and functional ROIs defined on the group average and therefore did not account for individual functional variability. Second, a few subjects (five in the LTMP group and four in the RTMP group) had task-related activity in the RTMP ROI before TMS. No correlation was found, however, between the fMRI response in the RTMP ROI before rTMS and the fMRI response in the RTMP ROI after rTMS either for the LTMP group ($R^2 = .01$, $p = .7$) or for the RTMP group ($R^2 = .04$, $p = .5$). In addition, we also examined changes in fMRI response over time in the four ROIs for both groups. Task-related fMRI response was measured in three 5.3-min blocks pre- and post-rTMS and assessed for each ROI (i.e., LTMP, RTMP, LIFG, RIFG). No effect of time was found, $F(1, 11) = 0.02$, $p = .9$. Finally, no correlations between the changes in RT and the changes in fMRI response in any of the four ROIs were found after rTMS, indicating that the functional disruption caused by TMS might not have recovered after the 16 min scan.

Conclusion

Taken together, these findings complement previous work on the interhemispheric reorganization of language processing after rTMS-induced interference and add to the literature about the role of homologue areas in the contralateral hemisphere in the language-related network.

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