

## Priming Frequencies of Transcranial Magnetic Stimulation over Wernicke's Area Modulate Word Detection

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**Priming stimulations have shown powerful effects on motor cortex behavior. However, the effects over language areas have not been explored. We assessed the effects of different priming frequencies of repetitive transcranial magnetic stimulation (rTMS), 1 Hz rTMS or 50 Hz bursts of rTMS (theta burst stimulation [TBS]), on temporoparietal language areas (i.e., Wernicke's area) localized with functional magnetic resonance imaging. Functional maps were acquired during an auditory word-detection task with native or foreign language sentences in 14 healthy men. Frameless stereotaxy was used to guide the transcranial magnetic stimulation coil position over Wernicke's area. Active and placebo randomized sessions of priming stimulations (1 Hz rTMS or TBS) were applied at rest, and response times (RTs) were recorded during the auditory word-detection task performed subsequently with 1 Hz rTMS. Individual anatomofunctional maps localized activation in Wernicke's area. Repeated-measure analysis of variance for RTs revealed that priming with 1 Hz rTMS facilitated the detection of native words, whereas priming with TBS facilitated the detection of foreign words. Consistent with motor cortex studies, these findings suggest that priming frequency plays a crucial role in word detection in the auditory stream.**

**Keywords:** functional magnetic resonance imaging, theta burst stimulation, transcranial magnetic stimulation, Wernicke's area

### Introduction

Stimulation frequency is a major factor in the variability of transcranial magnetic stimulation (TMS) effects (Wassermann 2002). The basis of TMS is electromagnetic induction, in which a time-varying magnetic field generated by a conductive coil induces an electric current in the cortex beneath the coil (Barker et al. 1985). By inducing a temporary and reversible virtual lesion, TMS interferes with neuronal activity and allows to determine the relationship between the stimulated area and associated behavioral changes.

To date, the modulatory effects of TMS on cortical excitability have been shown to depend on the frequency, intensity, duration, and intertrain interval (Chen et al. 1997; Berardelli et al. 1998; Pascual-Leone et al. 1998). Stimulation frequency has been reported to induce different effects on motor cortical excitability, with low frequency (<1 Hz) causing inhibitory effects and high frequency (>1 Hz) causing facilitatory effects (Wassermann et al. 1998; Maeda et al. 2000; Gorsler et al. 2003). However, these bidirectional effects of high- and low-frequency

repetitive transcranial magnetic stimulation (rTMS) are controversial because several studies have reported no change in intracortical inhibition (ICI) or intracortical facilitation (Gilio et al. 2003; Gorsler et al. 2003; Peineman et al. 2004; Daskalakis et al. 2006).

Besides these effects on motor cortex, the impact of TMS frequency on other brain regions, particularly on those involved in higher functions such as language, is unclear. Language processing is intricate and involves a network of interconnected areas (Poldrack et al. 1999; McDermott et al. 2003). High-frequency repetitive TMS (20 Hz rTMS) over the temporoparietal area (Wernicke's area) has been reported to facilitate picture naming (Mottaghy et al. 1999), whereas high-frequency rTMS over Broca's area facilitated phonologic processing (Nixon et al. 2004) or impaired semantic processing (Devlin et al. 2003; Thiel et al. 2005). Although facilitatory effects on linguistic performance have been found with high-frequency rTMS, a similar effect was recently reported with low-frequency 1 Hz rTMS (Andoh, Artiges, et al. 2006), suggesting that the role of rTMS frequency in the modulation of language processing deserves further investigation. Only one study has examined the effect of TMS frequency by comparing 1 Hz rTMS and 20 Hz rTMS applied before starting a language task. Performance facilitation was observed only with the 20-Hz frequency, and the reported TMS effects were small and did not last more than 2 min (Sparing et al. 2001).

Recently, Huang et al. (2005) have used a TMS protocol, which was modified from theta burst stimulation (TBS) protocols used in animal preparations to induce long-term potentiation (Abraham 2003). They found that TBS produced a consistent and powerful effect on motor cortex physiology and motor behavior.

Regarding language functions, no experiment has examined the effect of TBS protocols. We aimed to assess the role of frequency by examining the effect of extreme frequencies of rTMS, namely, TBS and 1 Hz rTMS, on the performance in a word-detection task.

However, as an experimental design, comparing TBS and 1 Hz rTMS directly during the language task would not avoid nonspecific effects (e.g., attentional effects due to noise, different intersensory effects of TBS, and 1 Hz rTMS), and considering that the number of pulses would differ if TBS and 1 Hz rTMS series were applied during the same period of time, alternative designs using a "priming" method might be

interesting. Indeed, Iyer et al. (2003) used this approach, first stimulating the motor cortex with high-frequency stimulation (6 Hz) and then with a 1-Hz rTMS series (i.e., 6 Hz priming 1 Hz rTMS). An advantage of this priming method is the possibility to study the effects of different priming frequencies on subsequent identical rTMS frequencies. Therefore, such a design can be used to modulate the facilitatory effect of 1 Hz rTMS on linguistic performance (i.e., decreased response time [RT]) that we previously reported (Andoh, Artiges, et al. 2006).

In the present study, we compared 2 extremes of priming frequencies of rTMS on the performance in a word-detection task with French and foreign languages stimuli, while low-frequency rTMS was applied over Wernicke's area. Andoh, Artiges, et al. (2006) found that 1 Hz rTMS applied over Wernicke's area facilitated the detection in French stimuli more than in foreign stimuli. In the present experiment, we expected 1 Hz rTMS priming to improve again performance on French stimuli. The putative effect of TBS priming could hardly be predicted because no previous study examined its cognitive effects. Potentiation could be hypothesized by analogy with its reported effects on motor-evoked potentials (Huang et al. 2005).

## Subjects and Methods

### Subjects

Fourteen healthy male subjects (mean age,  $24 \pm 4$  years old) gave written informed consent for the study, which was approved by the Paris-Pitié-Salpêtrière ethics committee. They were native French speakers, unfamiliar with Polish, Korean, or Japanese languages, and right handed according to the questionnaire of Annett (1967) (range 90-100%, mean  $97.1 \pm 3.3\%$ ). Their educational level was homogeneous ( $10.1 \pm 1.4$  years of education), with no history of neurological disease, head injury, or hearing impairment. TMS sessions were performed according to the safety guidelines (Wassermann 1996), and TBS priming was based on previous motor cortex studies (Huang and Rothwell 2004; Huang et al. 2005).

### Task Description

The language task developed by Pallier et al. (2003) was used in both functional magnetic resonance imaging (fMRI) and TMS sessions (see

Fig. 1A). The participants listened to sentences in their native language (French) and in languages unknown to them (Korean, Polish, and Japanese) and were required to perform a speech fragment detection task. Following each 3 s sentence and after a 0.5-s delay, a fragment of 0.5 s was played and the participants had to press one of 2 response buttons to indicate whether or not the fragment 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.

To increase the reliance of the subjects on the semantic level in the case of French stimuli, the fragments corresponded to words, making the task effectively a "word-detection" task for French stimuli. The intertrial interval was 7 s. Languages and sides of response were presented in a different randomized order for each subject. A PC computer running E-Prime® software (Psychology Software Tools Inc., Pittsburgh, PA) played the auditory stimuli and recorded the responses.

## Magnetic Resonance Imaging

### Anatomical MRI Acquisition

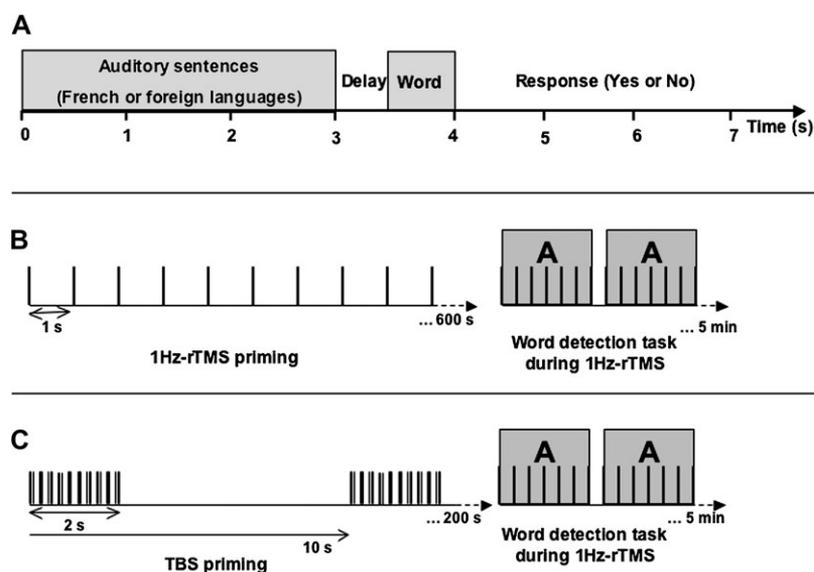
A  $T_1$ -weighted 3-dimensional (3D) image was acquired for each participant with a high-resolution head array coil (8-channel design, 1.5T GE Signa scanner, General Electric, Milwaukee) using a fast gradient-echo sequence (field of view [FOV] =  $24 \times 18$  cm, and a  $256 \times 192$  matrix size, resulting in  $0.94 \times 0.94 \times 1.3$  mm thick voxels).

### fMRI Acquisition

Before scanning, subjects performed a practice run of 10 trials. A gradient-echo echo-planar imaging pulse sequence was then acquired in an interleaved sequence (20 slices,  $3.75 \times 3.75 \times 5$  mm, and a  $64 \times 64$  matrix size, time repetition = 2000 ms, time echo = 60 ms, FOV = 24 cm). Auditory events were synchronized using E-Prime software with event-related fMRI volume acquisitions and were administered in two 14-min sessions of 108 randomized trials (54 French sentences, 54 foreign language sentences). Two sessions with 420 functional images (=840) were acquired for each subject. The first 4 images were excluded from the analyses to allow for stability in magnetization.

### fMRI Data Analyses

Functional time series data were processed using SPM2 and MATLAB® 6.5. Preprocessing of functional time series included slice timing and



**Figure 1.** Schemata of the word-detection task used during fMRI or after priming rTMS procedures. (A) Word-detection task. Participants listened to sentences in their native language and in languages unknown to them. They had to press right or left thumb response buttons depending on whether or not a 0.5-s entire word was present in the sentence just heard. (B) 1 Hz rTMS priming 1 Hz rTMS (900 pulses). The 1-Hz rTMS priming was applied over 600 s (600 pulses). The subsequent 1 Hz rTMS was applied during a 5-min word-detection task (300 pulses). (C) TBS priming 1 Hz rTMS (900 pulses). Three pulses of 50 Hz stimulation, repeated every 0.2 s over 2 s, were given. Each 2 s train of TBS was repeated every 10 s for a total of 200 s (600 pulses). A subsequent 1 Hz rTMS was applied during a 5-min word-detection task (300 pulses).

spatial realignment (correction of movements). The functional time series data were then normalized using nonlinear spatial normalization to the stereotaxic space devised by the Montreal Neurological Institute based on the  $T_1$  structural images of each subject. Finally, each image was smoothed with a 5-mm full-width half-maximum Gaussian filter.

For statistical analyses, we generated 2 separate linear models. One model was defined by right and left motor responses, and the other model was defined by French and foreign sentences.

The blood oxygen level-dependent response to the stimulus onset for each event type was convolved with the hemodynamic response function and its temporal derivative to account for small temporal shifts in the response to the stimuli (Friston et al. 1998). Six covariates were also included for each session in order to capture residual movement-related artifacts (the 3 rigid-body translations and the 3 rotations determined from initial registration), and a single covariate representing the mean (constant) over scans was added.

Images of parameter estimates for each contrast of interest were created for each subject for 1) detection of right thumb motor activation from the  $t$ -contrast ( $t$ -map) between right and left thumb movements; 2) determination of the areas where French elicited stronger activation than foreign words; 3) an exploratory analysis investigating the areas where foreign words produced stronger activation than French.

The coordinates of the maximum fMRI activation (peak voxel) within the activated regions (in particular, in the posterior temporal Wernicke's area) were obtained and converted using an algorithm (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) to relate the peak coordinates to the atlas of Talairach and Tournoux (1988). Individual activation maps (see Fig. 2A), defined as separate activated clusters on each subject's functional map, were identified according to their  $x$ ,  $y$ , or  $z$  Talairach's coordinates and their corresponding anatomical landmarks.

#### Determination of the TMS Sites from Magnetic Resonance Images

The  $t$ -maps constructed from fMRI data (defined in Talairach's space) described above (i.e., right thumb and Wernicke's areas) were transformed in the subject's MRI space using a reversed native-to-Talairach's transformation matrix. Afterward, Brainvisa software (<http://brainvisa.info>) was used to project the voxel corresponding to the local maximum of the activation cluster (right thumb and Wernicke's area) perpendicularly onto the 3D head rendering (see Fig. 2B). Because of inaccuracies in head surface reconstruction that may induce local geometric artifacts confounding target projection on the head surface, the closest scalp point may not be the optimal target position, while the barycenter of the 10 closest scalp points minimizes the deviation. Hence, for a voxel maximum located in the cortex, Brainvisa software automatically provided the closest barycenter on the head surface as the optimal coil position for TMS stimulation (see Fig. 2C; Andoh, Artiges, et al. 2006; Andoh, Cachia, et al. 2006).

#### Transcranial Magnetic Stimulation

##### TMS Procedure

The TMS experiment took place a few days after MRI data acquisition. A real-time optically tracked frameless stereotaxic system (Brainsight™

Frameless) plugged into Brainvisa software (<http://brainvisa.info>) was used in real time to guide the optimal coil position over the subject's scalp. TMS was applied using a MagPro X100 stimulator (Medtronic-Dantec®, Skovlunde, Denmark; <http://www.medtronic.com>) with an 8-shaped coil (each wing 50 mm in diameter, maximum magnetic field 2.5 T).

A placebo coil (Medtronic-Dantec®) was also used to reproduce the same acoustic stimulation as the active coil without inducing a magnetic field. The subjects were unaware of the stimulation mode used (active or placebo).

##### Motor Threshold Determination

The optimal functional target of the right thumb obtained from MRI allowed easy and rapid coil positioning. The motor threshold (MT) was defined as the minimal intensity of stimulator output required to elicit a motor-evoked potential (MEP) >50  $\mu$ V in the relaxed abductor pollicis brevis on 5 out of 10 consecutive trials (Rothwell et al. 1999). MTs were between 35% and 70% of maximum stimulator output (mean  $57 \pm 8\%$ ).

##### Experimental Procedure of Priming Stimulation Frequencies

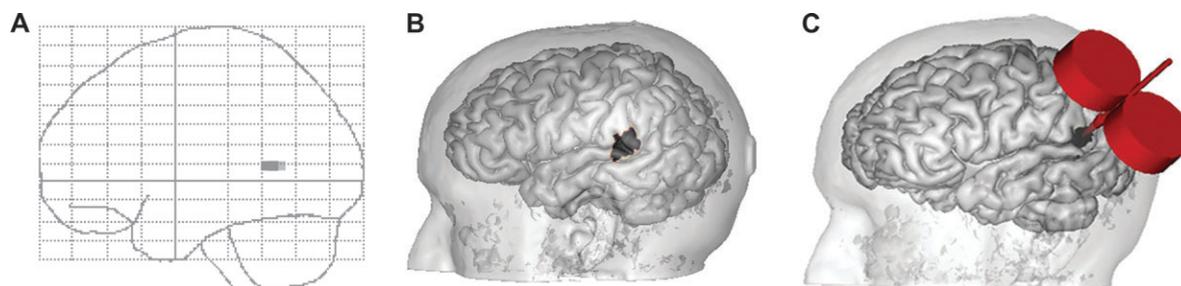
A 3-min practice session with the word-detection task (identical to that used for fMRI acquisition) was done without any stimulation. Four randomized stimulation sessions were then administered to all subjects:

1. Two sessions (one active, one placebo) of 1 Hz rTMS priming 1 Hz rTMS (see Fig. 1B). The 1-Hz rTMS priming session consisted of 1 Hz pulses at 110% MT over 10 min (total of 600 pulses). A 1-Hz rTMS at 110% MT was subsequently applied during a 5-min word-detection task.
2. Two sessions (one active, one placebo) of TBS priming 1 Hz rTMS (see Fig. 1C). The TBS pattern consisted of bursts (at 90% MT) of 3 pulses at 50 Hz (20 ms between each pulse), which were repeated at 200 ms intervals (i.e., 5 Hz) over 2 s. This 2 s TBS train was repeated every 10 s for a total of 200 s (i.e., 600 pulses). A 1-Hz rTMS (at 110% MT) was subsequently applied during a 5-min word-detection task.

Each stimulation session was followed by a 30-min rest interval to avoid carry over effects from one block to the next (Huang et al. 2005). Auditory events, identical to those used in the fMRI acquisition, were presented via earphones and synchronized with the rTMS trains. A PC running E-Prime software was connected to the TMS stimulator to trigger and control the timing of stimulation trains. The percentage of correct responses (accuracy) and the mean RT were calculated for each condition. The order of priming stimulation frequencies (1 Hz rTMS and TBS) and stimulation modes (active or placebo) was randomized across subjects.

##### Statistical Analysis of Behavioral Data

Statistical analyses were performed using StatView® 5.0 software (SAS Institute, <http://www.statview.com>). The mean RT was analyzed using repeated-measures analysis of variance (ANOVA) with 3 within-subject factors: priming stimulation frequencies (1 Hz rTMS, TBS), stimulation mode (placebo, active), and language (French, foreign words). Paired  $t$ -tests were used for post hoc analysis.



**Figure 2.** Wernicke's area definition using fMRI. (A) Individual statistical parametrical map for the fMRI subtraction "French minus foreign words." The cortex cluster with the highest  $t$ -value was clearly visible in each subject and corresponded to Wernicke's area in the subject displayed (peak voxel at  $-53, -65, 10; Z > 8$ ) in the atlas of Talairach and Tournoux (1988). (B) Brainvisa software was used to map the cluster of maximal activity onto the subject's unnormalized 3D cortex rendering and (C) to guide coil positioning over Wernicke's area on a 3D head surface.

## Results

### fMRI Results

fMRI data from one subject did not show any activation and was excluded from the analyses.

To assess interindividual variability, mean individual fMRI activations for motor and language activations were mapped into Talairach's space. The statistical parametrical map (SPM) reflecting thumb movement activity detected a clear activation of the left motor cortex (Brodmann area [BA] 4) in each of the 13 subjects.

Posterior sylvian clusters of activation resulting from the French minus foreign sentences contrast were detected in each subject. *t*-maps were thresholded at  $P < 10^{-9}$  (family wise error corrected for multiple comparisons) (see Table 1). Significant activation was detected in the left middle temporal gyrus in all 13 subjects (mean  $\pm$  standard deviation [SD] peak voxel *x*, *y*, *z* Talairach's coordinates in mm:  $-49 \pm 5$ ,  $-44 \pm 14$ ,  $-1 \pm 7$ ;  $Z > 8$ ; extent:  $3594 \pm 3121$  mm<sup>3</sup>). Significant activation was also detected in the left superior temporal gyrus in 6 subjects (mean  $\pm$  SD peak voxel *x*, *y*, *z* Talairach's coordinates in mm:  $-52 \pm 20$ ,  $-32 \pm 19$ ,  $6 \pm 10$ ;  $Z > 8$ ; extent:  $3253 \pm 3977$  mm<sup>3</sup>). Group peak voxel Talairach's coordinates of Wernicke's area were *x*, *y*, *z*:  $-47 \pm 5$ ,  $-47 \pm 11$ ,  $3 \pm 10$  ( $Z > 8$ ; extent  $3633 \pm 3092$  mm<sup>3</sup>); maximum intersubject variations reached 10, 42, and 38 mm, respectively. Activation was also observed in the left inferior frontal gyrus (Broca's area) in 8 subjects, including the pars opercularis (POp) and/or the pars triangularis (PTr). Five subjects activated the POp (mean peak voxel at  $-48 \pm 7$ ,  $7 \pm 3$ ,  $17 \pm 9$ ;  $Z > 8$ ; extent:  $1856 \pm 1072$  mm<sup>3</sup>) and 3 subjects activated the PTr (mean peak voxel at  $-48 \pm 4$ ,  $16 \pm 4$ ,  $-2 \pm 5$ ;  $Z > 8$ ; extent  $8128 \pm 10055$  mm<sup>3</sup>). The right middle temporal gyrus was activated in only 5 subjects (mean peak voxel at  $43 \pm 9$ ,  $-38 \pm 11$ ,  $-0 \pm 11$ ;  $Z > 5.9$ ; extent:  $4416 \pm 4041$  mm<sup>3</sup>).

The contrast foreign sentences minus French was also explored for each subject at the voxelwise threshold of  $P < 0.001$  uncorrected and the  $P < 0.05$  threshold on the extent of clusters. Eleven subjects activated the left lateral frontal cortex within the middle frontal gyrus (mean peak voxel at  $-29 \pm 7$ ,  $26 \pm 15$ ,  $40 \pm 8$ ;  $Z > 3.88$ ; extent:  $16721 \pm 29926$  mm<sup>3</sup>). Seven subjects activated the left superior frontal cortex (mean peak voxel at  $-18 \pm 5$ ,  $45 \pm 9$ ,  $28 \pm 15$ ;  $Z > 4.01$ ; extent:  $23022 \pm 36386$

mm<sup>3</sup>). Significant activation was also detected in the left inferior parietal lobule in 10 subjects (mean peak voxel at  $-48 \pm 8$ ,  $-54 \pm 12$ ,  $34 \pm 6$ ;  $Z > 4.47$ ; extent:  $8186 \pm 7267$  mm<sup>3</sup>). The right lateral frontal cortex was also activated in 8 subjects (mean peak voxel at  $33 \pm 7$ ,  $29 \pm 18$ ,  $32 \pm 23$ ;  $Z > 4.78$ ; extent:  $5530 \pm 7751$  mm<sup>3</sup>), the right superior frontal cortex in 6 subjects (mean peak voxel at  $17 \pm 0$ ,  $28 \pm 14$ ,  $43 \pm 4$ ;  $Z > 3.84$ ; extent:  $5530 \pm 7751$  mm<sup>3</sup>), and the right inferior parietal regions in 4 subjects (mean peak voxel at  $34 \pm 11$ ,  $-53 \pm 5$ ,  $37 \pm 2$ ;  $Z > 3.72$ ; extent:  $2144 \pm 2858$  mm<sup>3</sup>).

### TMS Effects on the Targeted Wernicke's Area

One subject reported headache caused by active TBS. However his mean RT for this stimulation [1269 ms for French and 1185 ms for foreign words] was within the RT range of the subjects' samples [535 to 1295 ms for French and 849 to 1348 ms for foreign words].

Regarding general effects, a significant effect of language was detected for RT ( $F_{1,2} = 28.86$ ,  $P = 0.0002$ ) indicating that RT for foreign words was slower than RT for French. There was a significant main effect of stimulation mode on RT ( $F_{1,2} = 7.7$ ,  $P = 0.01$ ), namely, RT for active stimulation was faster ( $1020 \pm 30$  ms) relative to placebo stimulation ( $1066 \pm 31$  ms). There was also an interaction between priming stimulation frequencies and language ( $F_{1,2} = 7.42$ ,  $P < 0.02$ ). The interaction between priming stimulation frequencies, stimulation mode, and language was significant ( $F_{1,2} = 5.56$ ,  $P = 0.03$ ).

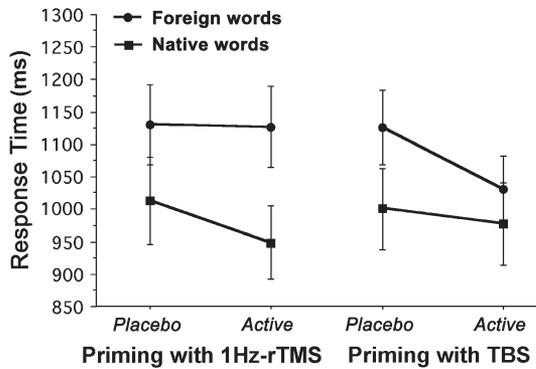
Separate ANOVAs were therefore conducted for each priming stimulation frequency. For "priming with 1 Hz rTMS," an interaction between stimulation mode and language ( $F_{1,2} = 4.5$ ,  $P = 0.05$ ) was found with a mean decrease of  $64 \pm 33$  ms for French and  $3 \pm 40$  ms for foreign words. For "priming with TBS," a significant interaction of stimulation mode  $\times$  language ( $F_{1,2} = 4.58$ ,  $P = 0.05$ ) indicated that active priming with TBS reduced RT for foreign words more than RT for French (mean decrease of  $95 \pm 27$  ms for foreign words and  $22 \pm 21$  ms for French; see Fig. 3). Placebo stimulations (baselines) of the 2 priming stimulation frequencies (1 Hz rTMS and TBS) did not differ (paired *t*-test:  $t > 0.35$ ,  $P = 0.73$ ).

Post hoc analyses revealed that for active stimulations, RTs for foreign words were decreased more for priming with TBS than for priming with 1 Hz rTMS (paired *t*-test:  $t > -2.37$ ,  $P = 0.03$ ), but

**Table 1**

Individual characteristics of posterior language area detected for French versus foreign sentences (voxelwise threshold of  $P < 10^{-9}$  corrected for multiple comparisons and at  $P < 10^{-4}$  threshold on the extent of clusters with more than 10 contiguous voxels)

Subjects	Talairach's coordinates (mm)			Voxel level		Cluster level	BA
	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value	Statistical parametrical map ( <i>Z</i> )	Extent (mm <sup>3</sup> )	
S1	-47	-42	-6	10.3	8	1088	21
S2	-46	-46	7	14.9	8	7104	21
S3	-39	-50	22	16.7	8	1728	22
S4	-50	-46	-2	12.3	8	1472	21
S5	-57	-42	-2	17.5	8	5056	21
S6	-53	-65	10	12.7	8	2816	39
S7	-43	-46	-6	15.8	8	3136	21
S8	-50	-27	-9	8.9	8	640	21
S9	-50	-54	4	14.4	8	1856	21
S10	-46	-46	1	16.8	8	11 456	21
S11	-46	-65	3	16.5	8	2240	37
S12	-39	-46	18	18.2	8	3520	22
S13	-43	-46	1	15.2	8	5952	21



**Figure 3.** Mean RTs pooled for 13 participants. Left, 1 Hz rTMS priming 1 Hz rTMS during a 5-min word-detection task; significant interaction of stimulation mode  $\times$  language ( $F_{1,12} = 4.5, P = 0.05$ ). Right, TBS priming 1 Hz rTMS during a 5-min word-detection task; significant interaction of stimulation mode  $\times$  language ( $F_{1,12} = 4.58, P = 0.05$ ). Error bars indicate standard error.

RTs for French did not differ significantly between priming with 1 Hz rTMS and priming with TBS (paired  $t$ -test:  $t > 1.6, P = 0.11$ ).

We detected a significant effect of language on error rates ( $F_{1,2} = 94.5, P < 0.0001$ ); participants had higher error rates for foreign words (25.7%) than for French words (3.4%). However, the error rate was not significantly modified by either priming stimulation frequency ( $F_{1,2} = 0.2, P = 0.63$ , not significant [NS]) or by stimulation mode ( $F_{1,2} = 0.83, P = 0.38$ , NS).

## Discussion

Two priming rTMS sequences differentially changed performance on a word-detection task during 1 Hz rTMS, using fMRI and neuronavigated TMS to target Wernicke's area. Priming with low-frequency 1 Hz rTMS decreased the RT more for native (French) than for foreign language words. A decrease in RT has previously been associated with a facilitation effect (Töpper et al. 1998; Mottaghy et al. 1999). Consistently, we recently reported an analogous decrease in RT with 1 Hz rTMS over Wernicke's area with no priming stimulations (Andoh, Artiges, et al. 2006). Therefore, both our previous and current results support a facilitation effect of low-frequency rTMS applied over the posterior STS (superior temporal sulcus)/inferior parietal cortices during auditory processing of native language.

In contrast, priming with TBS decreased RT for foreign words but not for French words. Intermittent TBS protocols have previously been used on the motor cortex (Huang et al. 2005) and have shown that TBS facilitated after-effects on MEPs evidenced by a significant increase (45%) in short-interval ICL. Here, TBS effect on cortical excitability of language areas was assessed indirectly using a behavioral measure (reaction time) in a randomized placebo-controlled study. The magnitude of the mean RT decrease was comparable to that observed by other investigators with the usual TMS frequencies during language tasks (Sakai et al. 2002; Devlin et al. 2003; Nixon et al. 2004). It could be raised that TBS nonspecifically facilitated foreign words. However, we could exclude facilitation due to the noise of active TBS because the placebo condition had no impact on RT. Other nonspecific effects related to tactile stimulation of the scalp during active TBS could also be excluded, as French words were not facilitated to the same degree as foreign words.

Although the effect of active TBS priming was objectively assessed, its interpretation remains intricate, requiring further research on priming stimulations and on TBS for a comprehen-

sive delineation. Nevertheless, we propose to interpret the observed dissociation between the effects of the 2 priming frequencies on the language task, within the context of both local and distant engaged brain regions.

Differential effects of the 2 priming frequencies highlight the role of rTMS frequency on the auditory word-detection stream and are consistent with TMS studies on the motor cortex (Wassermann et al. 1998; Maeda et al. 2000; Gorsler et al. 2003). A positron emission tomography study showed frequency dependent changes in regional cerebral blood flow and connectivity following rTMS over the primary motor cortex (Rounis et al. 2005). Hence, it might be hypothesized that propagated TMS-induced effects in regions connected with Wernicke's area may depend on stimulation frequency. We speculate that such connected regions are engaged in the detection of foreign words during the word-detection task. fMRI activation related to the image subtraction foreign words minus French showed bilateral activation in the inferior parietal region (BA 40) and in the superior, medial, and lateral frontal regions (BA 8/9). Activation of these regions has previously been linked to language processes involved in the word-detection task used in this study. Phonological processing, short-term memory, and sequencing of phonemes have been reported to engage the left inferior parietal region (BA 40) (Paulesu et al. 1993; Gelfand and Bookheimer 2003; Jacquemot et al. 2003), whereas whole-word phonology engaged the frontal lobes of both hemispheres (BA 8/9) (Booth et al. 2006). Paralinguistic aspects of speech, including decoding of nonverbal emotional information in the voice (i.e., prosody) have also implicated these frontal areas (Kotz et al. 2003; Barrett et al. 2004; Ethofer et al. 2005). A putative mechanism to account for enhanced phonologic/prosodic processing when stimulating Wernicke's area could be the change in activity in the interconnected frontal/parietal regions that were activated by the present word-detection task. This hypothesis could be examined by further studies on rTMS-induced changes in activity of the stimulated areas and on propagated effects in remote interconnected areas.

## Limitations

An alternative design could have used 1 Hz rTMS or TBS series before the task without priming a second 1 Hz rTMS series. However, such a design would have differed from that used in our previous study, which indicated a facilitatory effect of 1 Hz rTMS applied while the subjects were engaged in the task (Andoh, Artiges, et al. 2006). The present TMS design (high-frequency priming a low-frequency rTMS series) was based on a previous report (Iyer et al. 2003); 3 limitations or particularities influencing the interpretation of results should be considered. First, the intensity of the priming stimulations differed in TBS and 1 Hz rTMS conditions. Intensity was set at 110% MT for 1 Hz rTMS, consistent with our previous study (Andoh, Artiges, et al. 2006), and at 90% MT for TBS, consistent with the subjects' tolerance levels and safety recommendations for TBS on motor cortex (Huang et al. 2005). Second, we did not assess the duration of stimulation after-effects, which could have lasted from one rTMS session to the following one. However, we did randomize active and placebo stimulations, and the 30-min rest intervals were based on previous motor cortex TBS results (Huang et al. 2005).

Finally, we used a neuronavigation system to help to locate the coil, but we did not control for the variable depth of the

targeted region. However, we did use Brainvisa software to verify in real time that Wernicke's target was <2 cm below the coil (Bohning et al. 2001).

## Conclusion

This is the first study using TBS to modulate language functions and reporting a role for priming frequencies of rTMS on the modulation of language processing. The results suggest that stimulation frequency may play a crucial role in word detection in the auditory stream.

## Notes

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