Behavioral/Systems/Cognitive

Transient Functional Suppression and Facilitation of Japanese Ideogram Writing Induced by Repetitive Transcranial Magnetic Stimulation of Posterior Inferior Temporal Cortex

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The Japanese writing system is unique in that it is composed of two different orthographies: kanji (morphograms) and kana (syllabograms). The retrieval of the visual orthographic representations of Japanese kanji is crucial to the process of writing in Japanese. We used low-frequency repetitive transcranial magnetic stimulation (rTMS) to clarify the functional relevance of the left and right posterior inferior temporal cortex (PITC) to this process in native Japanese speakers. The experimental paradigms included the mental recall of kanji, kana-to-kanji transcription, semantic judgment, oral reading, and copying of kana and kanji. The first two tasks require the visualization of the kanji image of the word. We applied 0.9 Hz rTMS (600 total pulses) over individually determined left or right PITC to suppress cortical activity and measured subsequent task performance. In the mental recall of kanji and kana-to-kanji transcription, rTMS over the left PITC prolonged reaction times (RTs), whereas rTMS over the right PITC reduced RTs. In the other tasks, which do not involve the mental visualization of kanji, rTMS over the left or right PITC had no effect on performance. These results suggest that the left PITC is crucial for the retrieval of the visual graphic representation of kanji. Furthermore, the right PITC may work to suppress the dominant left PITC in the neural network for kanji writing, which involves visual word recognition.

Key words: Japanese ideogram writing; kanji; visual word recognition; posterior inferior temporal cortex; PITC; repetitive transcranial magnetic stimulation; rTMS; interhemispheric neural networks

Introduction

In the West, many patient studies, beginning with that of Déjerine, have established that lesions of the left angular gyrus produce writing disturbances associated with reading impairments (alexia with agraphia) (Dejerine, 1891; Geschwind, 1965). Later, another type of agraphia was described: damage to the junction of the left angular gyrus and the parieto-occipital lobule produces lexical agraphia. This damage is attributable to a disruption in the whole-word retrieval system necessary to read orthographically irregular words (Roeltgen et al., 1983; Roeltgen and Heilman, 1984; Roeltgen, 1993). The study of functional differences in left

hemisphere writing systems has thus, as yet, been based solely on studies of Western languages.

The Japanese writing system is unique in that it is composed of two different orthographies: kanji (morphograms) and kana (syllabograms). Because kanji characters are complex graphic forms that are associated with semantics as well as multiple phonetic representations, kanji writing requires the selection of a contextually appropriate lexical item from among several homophone candidates stored in orthographic memory. In contrast, kana characters have only phonological meanings, comparable with the Western alphabet.

Japanese patients with lesions in the left angular gyrus show alexia of kana with agraphia of both kana and kanji, whereas lesions in the left posterior inferior temporal cortex (PITC) result in alexia with agraphia for kanji only (Yamadori, 1975, 2000; Kawamura et al., 1987; Kawahata et al., 1988; Soma et al., 1989; Sakurai et al., 1994). Recent functional neuroimaging studies have shown that language tasks involving kanji, especially kanji writing and the mental retrieval of images, activate the left PITC (Tokunaga et al., 1999; Nakamura et al., 2000; Sakurai et al., 2000). Thus, kanji and kana writing systems may involve different subprocesses in the left hemisphere. The left PITC may be

involved in kanji writing processing, particularly the subprocess of accessing the visual graphic kanji images stored in long-term memory (Iwata, 1984).

Low-frequency repetitive transcranial magnetic stimulation (rTMS) at ~1 Hz can produce focal and transient disruption of cortical function that lasts beyond the duration of the stimulus train (Chen et al., 1997; Walsh and Cowey, 1998; Pascual-Leone et al., 1999). This inhibitory effect of rTMS is caused by the transient suppression of cortical excitability in the focal region in which rTMS was delivered (Chen et al., 1997; Kosslyn et al., 1999; Satow et al., 2003). This technique has been used to show whether a given brain region is essential for a particular cognitive process (Walsh and Rushworth, 1999). Thus, based on neuroimaging studies, we can evaluate the relationship between the targeted cortical region and a particular type of brain processing.

By using low-frequency rTMS in normal volunteers, we examined whether the left PITC is crucial to the retrieval of visual orthographic kanji representations, which is a process necessary during writing. Second, we investigated the potential role of the right PITC in writing kanji. This latter issue has rarely been addressed, and its elucidation could contribute to the development of new therapies for aphasia (Martin et al., 2004).

Materials and Methods
Subjects
Seventeen healthy volunteers (13 males and 4 females, aged 27.5 ± 5.0 years, mean ± SD) were involved in the study. All were native Japanese speakers and right-handed, as confirmed by the Edinburgh inventory. None had a history of psychiatric or neurological disease. Subjects were fully instructed regarding the details of the study and gave written informed consent before the experiment. The protocol was in accordance with the guidelines determined by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (protocol number 267).

Word stimuli
One hundred twenty-eight two-character compound kanji words were selected from the fundamental vocabulary for the teaching of the Japanese language. When spelled in kana, the words consisted of two to six kana characters. Kana scripts corresponding to the selected kanji words were also used as stimuli. Half of the 128 words represented concrete nouns and the other half abstract nouns. There were no homophones. The level of concreteness and imagery of most words exceeded level 6 based on the 7-level scales of concreteness and imagery (Ogawa and Inamura, 1974). In most cases, the lexical frequency of the words exceeded 500 per 1,000,000. All of the words used in this study are conventionally spelled in kanji in daily life. A set of 32 words in kanji and 32 words in kana were randomly selected from the 128 words for each session. Each word was presented in white, horizontally in the center of a black screen located 100 cm in front of subjects (visual angle of 0.9–2.6°). Each kanji or kana word was presented only once during a session. Each stimulus was presented for 400 ms, and the interstimulus interval (onset to onset) was 2500 ms. In each session, subjects had to perform one of the six predetermined tasks described below. They were instructed to perform the tasks as quickly and accurately as possible, immediately after each stimulus appeared.

Behavioral tasks
Each subject completed six behavioral tasks, including the mental recall of kanji orthography, kana-to-kanji transcription, semantic judgment, oral reading, and copying kana and kanji (Fig. 1). These tasks are similar to those used in a previous study (Nakamura et al., 2000).
a: Mental recall of kanji. Some kanji characters are composed of two radicals that are juxtaposed horizontally (L–R type), whereas others are not arranged according to this rule (non-L–R type). In this task, subjects responded by pressing one of two buttons: button 1 or 2, with the index or middle finger, respectively, of the right-hand. We instructed subjects to mentally transcribe each kana word into kanji script and press button
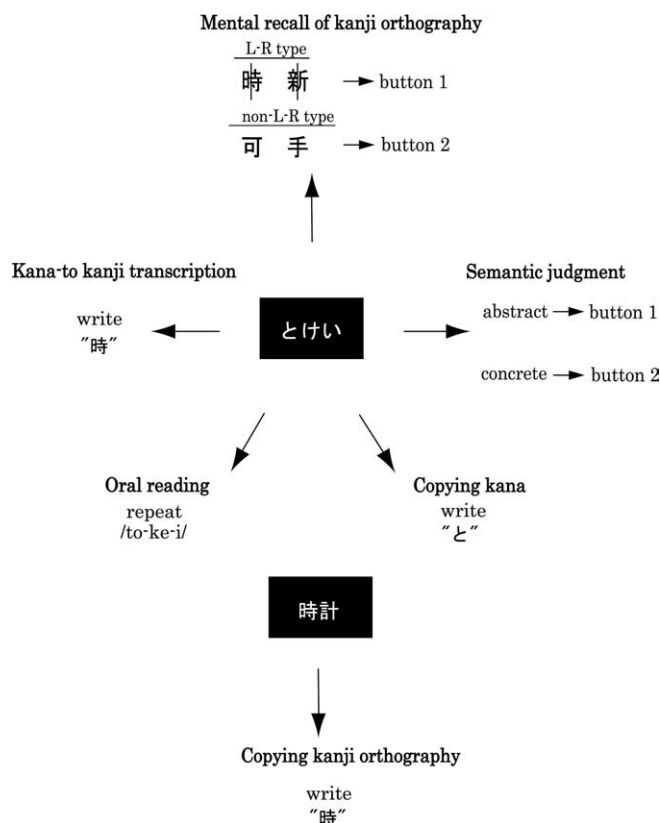

Figure 1. Stimulus materials and behavioral paradigms. Kana or kanji scripts for each word were presented horizontally on the screen: kana in five tasks (mental recall of kanji, kana-to-kanji transcription, semantic judgment, oral reading, and copying kana) and kanji in one task (copying kanji). In the mental recall of kanji (task a), subjects mentally transcribed each kana-to-kanji script and judged whether the first (left) kanji character could be divided into two sides according to whether it possessed side radicals or not. In the kana-to-kanji transcription (task b), subjects wrote the first kanji character on a board. In the semantic judgment task (task c), subjects decided whether the kana denoted concrete or abstract concepts. In the oral reading task (task d), subjects read kana aloud. When copying kana (task e) or kanji (task f), subjects copied the first (leftmost) character of the corresponding kanji or kana onto a board.

1 if the first (left) character of the kanji pair was the L–R type and button 2 if it was the non-L–R type. Each type occurred 50% of the time.
b: Kana-to-kanji transcription. On presentation of each kana word, the subjects were asked to write the first character of the corresponding kanji word on a board with their right hand using a pen. The board was attached to a force transducer (3000 Hz recordable) that detected changes in writing pressure.
c: Semantic judgment. Subjects were asked to decide whether the presented kana nouns denoted concrete objects or abstract concepts. In this task, we instructed subjects to press button 1 if the stimulus was an abstract noun and button 2 if it was a concrete noun. Each type of noun occurred 50% of the time.
d: Oral reading. Subjects were asked to read kana words aloud into a microphone.
e: Copying kana. Subjects copied the first (leftmost) character of a kana word on a board with the right hand.
f: Copying kanji. As in e, subjects copied the first character of a kanji word.
Thus, we used kana script for five of the tasks and kanji script for one task.

Transcranial magnetic stimulation
Surface electromyograms (EMGs) were recorded from the right first dorsal interosseous (FDI) muscle. The EMG signal was bandpass filtered (5–500 Hz) and digitized at the rate of 2000 Hz (SYNAMP; Neuroscan, Herndon, VA). The sampling rates for reaction times (RTs) in experi-
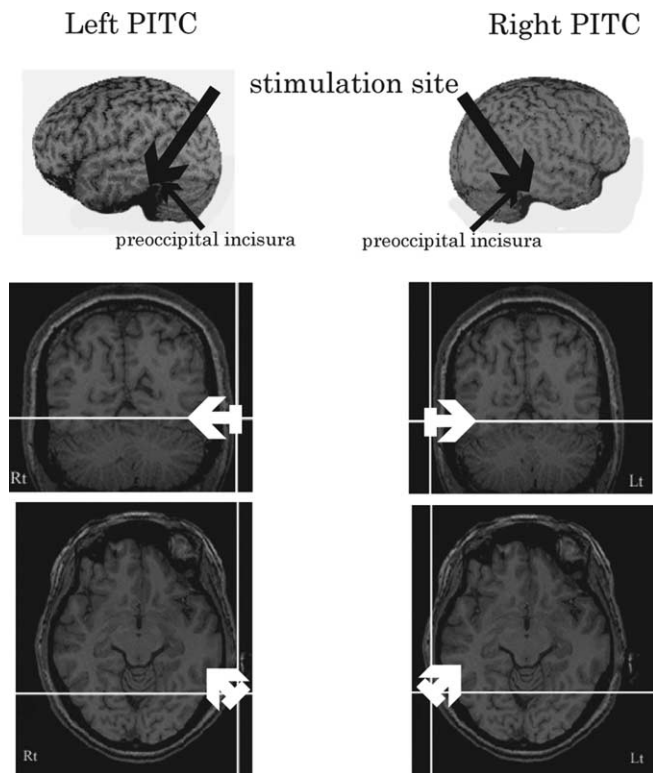
Figure 2. TMS stimulation sites for the left PITC and right PITC. The top, middle, and bottom panels show the three-dimensional surface brain reconstructions, and coronal and axial slices, respectively, of the MRI scans from one subject. In the top panels, the black thick arrows represent the coil stimulation site, and the direction of the arrows indicates the current flow induced by TMS in the brain on the three-dimensional MRI. The thin black arrows show the preoccipital incisura. In each of the middle and bottom panels, two perpendicular white lines are drawn, the intersection of which indicates the coil contact at which the induced electric field is at its maximum. The white thick lines indicate the orientation of the stimulation coil, and the white arrows represent the magnetic stimulation sites. Lt, Left; Rt, right.

ments 1–3 were 2000 Hz. TMS was performed with a Magstim Super Rapid Magnetic Stimulator (biphasic, pulse width of 250 μs) (Magstim, Whitland, Dyfed, UK) using an air-cooled figure-eight coil composed of two loops with an external diameter of 70 mm (maximum magnetic field strength, 0.93 tesla). The coil was placed over the optimal position in the left primary motor cortex to elicit the best motor response in the right FDI muscle. The resting motor threshold was defined as the lowest stimulus intensity required to elicit motor-evoked potentials with a peak-to-peak amplitude of >50 μV in the right FDI muscle in at least 5 of 10 trials (Rossini et al., 1994). In the present study, the rTMS stimulus intensity over the target area was fixed at 90% of the resting motor threshold for each individual subject and kept constant throughout the intervention. This TMS intensity was used to maximize the chance of local disruption of neural function without producing excessive discomfort (Mottaghy et al., 2002).

TMS stimulation site
TMS was applied to a region corresponding to the PITC of the left or right hemisphere on the basis of an anatomical magnetic resonance image of each subject. The magnetic resonance imaging (MRI) was conducted on a 3 or 0.2 tesla whole-body scanner equipped with a volume head coil [3 tesla (Trio; Siemens, Erlangen, Germany) or 0.2 tesla (Signa unit; General Electric, Milwaukee, WI)], and T1-weighted axial images were obtained. The TMS stimulation site was identified with a frameless stereotaxic system Brainsight (Rogue Research, Montreal, Quebec, Canada), which facilitates the positioning of the coil and allows the simultaneous visualization of the coil on a magnetic resonance image (Fig. 2). In the three-dimensional magnetic resonance image, to target the left PITC, we located the area 1 cm rostral to the left preoccipital incisura; this is

where peak activation was identified in our previous language study with functional MRI (fMRI) (Nakamura et al., 2000). With regard to the right PITC, we targeted the area 1 cm rostral to the right preoccipital incisura, because right PITC activation has been identified previously in the symmetrical right-hemisphere homolog of the left PITC (Cohen et al., 2002). On the scalp, the center of the coil position for PITC stimulation was located 2.5–3.0 cm dorsal and 9.0–12.0 cm lateral to the inion in the left hemisphere and 2.0–3.0 cm dorsal and 8.0–11.0 cm lateral to the right hemisphere inion.

Experimental procedures
The subjects were seated in an armchair with their arms placed on the armrests. In an experiment taking place during one day, rTMS was given at one target site and subjects performed two different tasks of all six tasks (tasks X and XX) before (pre-) and just after (post-) rTMS (total of four sessions) (Fig. 3). The behavioral parameters of the two different pre-rTMS tasks were used to measure the baseline performance of each task. The order of the two tasks in pre-rTMS and post-rTMS sessions was randomized across subjects to cancel the order effect. Because one session (32 trials) lasted <2 min and there was no interval between sessions 3 and 4 in post-rTMS, two sessions in post-rTMS (sessions 3 and 4) were completed within 5 min after rTMS had finished. This is important because the carryover effects of rTMS last half as long as the stimulation period (Chen et al., 1997; Muellbacher et al., 2000). The order that the two different tasks were given in pre-rTMS and post-rTMS was counterbalanced across subjects.

Experiment 1: stimulation of the PITC
To evaluate the functional relevance of the left and right PITC to the retrieval of the visual orthographic representation of kanji, rTMS was applied to the left or right PITC at a frequency of 0.9 Hz for 11 min (total of 600 pulses). The six tasks were divided into three sets of two tasks each: set 1 consisted of task a (mental recall of kanji) and task c (semantic judgment); set 2 was task b (kana-to-kanji transcription) and task d (oral reading); and set 3 was tasks e and f (copying kana and kanji, respectively). As described above, rTMS was given at either the left or right PITC, and one of the three sets of tasks was assigned to each subject. Therefore, the subjects performed two different tasks (tasks X and XX), each of which had pre-rTMS and post-rTMS sessions; this resulted in four sessions in total in one day (Fig. 3). In the experiment on the following day, rTMS was given to the opposite PITC while subjects performed the same task set. Ten subjects were involved in only one of each task set over 2 d: set 1 consisted of nine males and one female, aged 28.1 ± 6.2 years; set 2 was seven males and three females, aged 28.1 ± 5.5 years; and set 3 was seven males and two females, aged 26.1 ± 4.9 years. Some subjects repeated several sets of two tasks each in a different day each, i.e., seven subjects participated in two sets (four tasks in total), and four subjects completed three sets of tasks (six tasks total). To exclude the possible carryover effect, we performed the rTMS only once a day. Any two successive experiments were performed at least 3 d apart. The order of the participation in each of the three sets and the target sites for rTMS were randomized across subjects.

Experiment 2: stimulation of a control site in the left hemisphere
To investigate the regional specificity of the effect of rTMS over the left PITC, we applied rTMS over another location in the left hemisphere. We randomly selected six subjects from among the 10 subjects recruited for experiment 1 (five males and one female, aged 29.2 ± 6.2 years). All six or four subjects performed the same tasks, a and b (mental recall of kanji or kana-to-kanji transcription, respectively), as they had done in experiment 1. They participated in experiment 2 at least 1 month apart from experiment 1. We targeted a region 2 cm dorsal from the point of PITC stimulation on the scalp, whose coil position was determined using Brainsight. Because the responses in the mental recall of kanji and kana-to-kanji transcription tasks were significantly affected by rTMS over the left PITC in experiment 1, we chose only these tasks for experiment 2. The task order (two tasks) was randomized across subjects.

Experiment 3: sham stimulation over the right PITC
To confirm the possible contribution of learning to the facilitatory effect of rTMS, we performed control sham stimulation over the right PITC in

seven subjects, five of whom were randomly selected from among the subjects recruited for experiment 1 (five males and two females, aged 30.1 ± 3.4 years). Five or three subjects performed the same tasks, a or b, as the one in experiment 1. They participated in experiment 3 at least 1 month apart from experiment 1. Under the sham stimulation, a sham coil was positioned over the right PITC, and it produced a discharge click similar to that produced by the real rTMS, without producing a magnetic field. Subjects performed the mental recall of kanji and the kana-to-kanji transcription tasks in a single day. The order of the two tasks was randomized across subjects.

Analysis
For each trial, both response accuracy and behavioral performance were assessed. In the mental recall of kanji and the semantic judgment tasks, RT was measured by the timing of the button press after the stimulus onset. During oral reading, the subject's voice was recorded via a microphone, and the onset time of vocalization was used as the RT. In kana-to-kanji transcription and when copying kana and kanji script, the writing was recorded using a force transducer. The onset time of writing pressure was used as the RT. The responses of each subject were monitored with a video camera and scored both on-line and off-line.

For each session, the mean RT was calculated, and response accuracy was expressed as the percentage of correct answers (RA%). Trials in which there was no response for >2 s were marked as errors and excluded from the mean RT analysis.

To evaluate the effect of rTMS over the left and right PITC in experiment 1, the changes in mean RT and RA% were evaluated using a three-factor mixed-model ANOVA, task (tasks a–f), time (pre-rTMS or post-rTMS), and hemisphere (left or right PITC) as the main factors. The variance of the subjects was treated as a random effect. If the effect was significant, a *post hoc* test was performed to explore the strength of the main effects and patterns of interactions between factors. In experiments 2 and 3, to evaluate the different effects of rTMS over the site more dorsal to the left PITC and sham stimulation over the right PITC, changes in mean RT and RA% were examined for each session using paired *t* tests. The threshold of significance was set at $p < 0.05$.

Results
The resting motor threshold for the right FDI was 75.1 ± 8.1% of the maximal stimulator output. The actual stimulus intensity of rTMS was 67.8 ± 5.9% (mean ± SD).

Experiment 1: the effect of rTMS over the left or right PITC in all six tasks (Table 1)
Reaction times
Looking at the between-subjects effects, the three-factor ANOVA showed a significant main effect of task (*$p < 0.001$) but no significant main effect of side ($p = 0.89$) and time ($p = 0.25$). There was significant task by side interaction (*$p = 0.003$), side by time interaction (*$p = 0.001$), task by time interaction (*$p = 0.006$), and task by side by time interaction (*$p < 0.001$). Although there was no significant effect of the time contrast, the time factor showed interactions with task by side. Thus, we examined separate two-factor ANOVAs for each task independently, with side (left or right) and time (pre-rTMS or post-rTMS) as the between-subjects factor. In task a, mental recall of kanji, the ANOVA revealed a significant contrast for a time by side interaction (*$p = 0.001$) but no significant main effect of time ($p = 0.51$) and side ($p = 0.08$). The *post hoc* analysis comparing the effect of time revealed significantly prolonged RTs after rTMS in the left PITC (*$p = 0.01$) but significantly short-
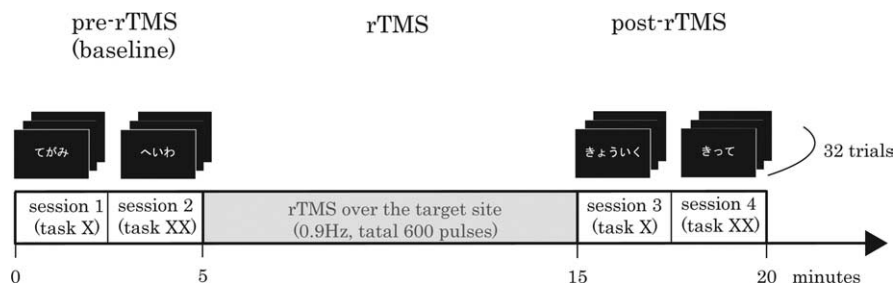

Figure 3. Experimental procedure. In an experiment taking place during one day, rTMS was given at one target site, and subjects performed two different tasks of all six tasks (task X and XX) before (pre-) and just after (post-) rTMS (total of four sessions). rTMS at 0.9 Hz (total of 600 pulses) was applied over the individually determined left or right PITC. The RTs and response accuracies were measured as behavioral parameters in each session and compared between the pre-rTMS and post-rTMS. Behavioral parameters of two tasks in pre-rTMS were used as the baseline of each task. The order of the two tasks in the pre-rTMS and post-rTMS sessions was randomized across subjects to cancel the order effect.

Table 1. Mean RTs and RA% in each of the six tasks before and after TMS over the left and right PITC

	Left PITC		Right PITC	
	Pre-TMS	Post-TMS	Pre-TMS	Post-TMS
RTs (ms)				
a	980 ± 180	1080 ± 170*	980 ± 140	910 ± 120*
b	700 ± 110	870 ± 120*	750 ± 160	660 ± 110*
c	950 ± 140	910 ± 130	960 ± 170	900 ± 170
d	490 ± 70	490 ± 60	560 ± 110	500 ± 60
e	390 ± 50	370 ± 50	380 ± 50	360 ± 60
f	430 ± 70	420 ± 40	440 ± 60	410 ± 60
RA%				
a	94.6 ± 6.3	89.0 ± 5.1*	92.4 ± 5.7	94.1 ± 4.0
b	97.2 ± 3.1	97.8 ± 2.6	98.1 ± 2.2	98.8 ± 2.2
c	90.0 ± 3.8	91.3 ± 4.1	90.3 ± 4.5	91.8 ± 5.0
d	100	100	100	100
e	100	100	100	100
f	100	100	100	100

*p values were produced using *post hoc* analyses comparing the mean level of RTs and RA% in each task between pre-rTMS and post-rTMS. a, Mental recall of kanji; b, kana-to-kanji transcription; c, semantic judgment; d, oral reading; e, copying kana; f, copying kanji.

ened RTs after rTMS in the right PITC (*$p = 0.04$). In task b, kana-to-kanji transcription, the ANOVA demonstrated a significant contrast for side (*$p = 0.02$), significant time by side interaction (*$p = 0.001$), but no significant effect of time ($p = 0.11$). The *post hoc* analysis comparing the effect of time demonstrated significantly prolonged RTs after rTMS in the left PITC (*$p = 0.003$) but significantly shortened RTs after rTMS in the right PITC (*$p = 0.02$). In task c (semantic judgment), task d (oral reading), task e (copying kana), and task f (copying kanji), ANOVAs revealed no significant contrast for time by side interaction (c, semantic judgment, $p = 0.65$; d, oral reading, $p = 0.22$; e, copying kana, $p = 0.47$; and f, copying kanji, $p = 0.74$).

Response accuracy
Several subjects claimed that they momentarily "forgot" letters during task a (mental recall of kanji) and task b (kana-to-kanji transcription) after rTMS.

Looking at the between-subjects effects, the three-factor ANOVA showed a significant main effect of task (*$p < 0.001$) but no significant main effect of side ($p = 0.10$) and time ($p = 0.94$). There was significant side by time interaction (*$p = 0.03$) and task by side by time interaction (*$p = 0.03$) but no significant task by time ($p = 0.10$) and task by side ($p = 0.80$) interaction. Although there was no significant effect of the time contrast, the time factor showed interactions with task by side. Thus, we examined separate two-factor ANOVAs for each task independ-
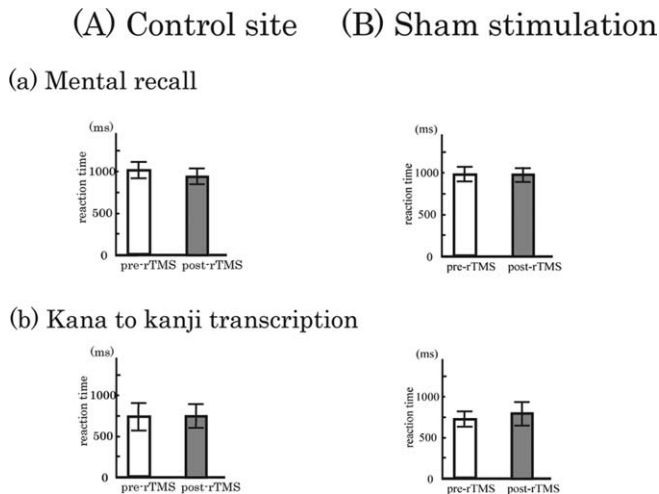
(A) Control site (B) Sham stimulation

(a) Mental recall

(b) Kana to kanji transcription

Figure 4. **A**, Effect of rTMS over the control site (2 cm dorsal to the left PITC) on RTs in the mental recall of kanji and kana-to-kanji transcription tasks. In task a (mental recall of kanji) and task b (kana-to-kanji transcription), rTMS over the control site had no effect on RTs. **B**, Effect of sham stimulation over the right PITC on RTs in the mental recall of kanji and kana-to-kanji transcription tasks. In both tasks a and b, there were no effects on RTs after sham stimulation.

dently, with side (left or right) and time (pre-rTMS or post-rTMS) as the between-subjects factor. In task a, mental recall of kanji, the ANOVA revealed a significant contrast for a time by side interaction (*$p = 0.02$) but no significant main effect of time ($p = 0.27$) and side ($p = 0.22$). The *post hoc* analysis comparing the effect of time revealed significantly decreased RA% after rTMS in the left PITC (*$p = 0.03$) but no effect in the right PITC ($p = 0.47$). In the task b (kana-to-kanji transcription) and task c (semantic judgment), the ANOVA revealed no significant contrast for time by side interaction (b, kana-to-kanji transcription, $p = 1.00$; c, semantic judgment, $p = 1.00$).

Experiment 2: effect of rTMS over the control site in the left hemisphere

When rTMS was delivered to the site 2 cm dorsal to the left PITC, the RTs after rTMS were not significantly different from those measured pre-rTMS for task a (mental recall of kanji, 1050 ± 140 ms pre-rTMS; 950 ± 110 ms post-rTMS; $p = 0.12$) or task b (kana-to-kanji transcription, 750 ± 160 ms pre-rTMS; 750 ± 130 ms post-rTMS; $p = 0.92$) (Fig. 4A). There were no effects on the RA% of rTMS of the control site for either task a ($96.9 \pm 5.1\%$ pre-rTMS; $95.6 \pm 5.1\%$ post-rTMS; $p = 0.84$) or task b ($99.5 \pm 1.3\%$ pre-rTMS; $99.0 \pm 2.6\%$ post-rTMS; $p = 0.36$).

Experiment 3: effect of sham stimulation over the right PITC

The RTs were not changed by sham stimulation for either task a (mental recall of kanji orthography, 990 ± 100 ms pre-rTMS; 980 ± 100 ms post-rTMS; $p = 0.90$) or task b (kana-to-kanji transcription, 740 ± 80 ms pre-rTMS; 790 ± 120 ms post-rTMS; $p = 0.62$) (Fig. 4B). The RA% scores were also unaffected by sham stimulation (task a, $93.7 \pm 4.4\%$ pre-rTMS, $94.7 \pm 3.9\%$ post-rTMS, $p = 0.62$; task b, $98.7 \pm 2.4\%$ pre-rTMS, $99.1 \pm 2.3\%$ post-rTMS, $p = 0.36$.

Regarding the variability of the baseline performance of tasks a and b across subject groups, there were no significant differences between experiments 1 and 2 or between experiments 1 and 3 for both RTs and RA%: for experiment 1 versus 2, $p = 0.45$ for RTs and $p = 0.82$ for RA%; for experiment 1 versus 3, $p = 0.89$ for RTs and $p = 0.76$ for RA% in task a; for experiment 1 versus 2,

$p = 0.41$ for RTs and $p = 0.11$ for RA%; for experiment 1 versus 3, $p = 0.41$ for RTs and $p = 0.31$ for RA% in task b (examined by Student's t test).

Discussion

The present study showed transient functional suppression and facilitation effects on Japanese kanji writing induced by low-frequency rTMS over the left and right PITC, respectively. The rTMS over the left PITC induced more errors and longer RTs in the tasks that required the visualization of kanji (the mental recall of kanji and kana-to-kanji transcription), suggesting that the left PITC is likely to be crucial for the mental retrieval of the graphic representation of kanji. In contrast, rTMS over the right PITC reduced RTs in the mental recall of kanji and kana-to-kanji transcription tasks, indicating that the nondominant PITC might work as a suppressor in the neural network required for writing kanji.

Functional role of the left PITC in kanji writing

In the mental recall of kanji task, we found a significantly lower RA% after rTMS over the left PITC. Additionally, rTMS over the left PITC resulted in longer RTs during the mental recall of kanji and kana-to-kanji transcription, which reflect the surplus time necessary to process these tasks as a result of the transient functional disruption of the left PITC. Because there is a trade-off between speed and accuracy in reaction time tasks, the longer RTs in these tasks after rTMS might have the same functional meaning as increased error rates. Because kana-to-kanji transcription is a highly skilled but almost automated procedure for normal Japanese adults, the transient functional depression of PITC could be easily compensated for by a small increase in RT, without leading to an increase in errors. Detailed psycholinguistic analysis based on the symptoms and lesion sites suggest that kanji-selective agraphia arises from an impaired access to visual graphic kanji images stored in long-term memory. This writing disorder is thought to be analogous to the lexical agraphia seen in Western languages (Roeltgen et al., 1983; Roeltgen and Heilman, 1984). Our findings complement the conventional view from lesion and fMRI studies that this area participates in the processing of kanji writing through orthographic retrieval, even with no accompanying overt motor execution (Soma et al., 1989; Nakamura et al., 2000).

In contrast, the RTs and RA% scores for the oral reading and semantic judgment tasks were not affected by rTMS, suggesting that the left PITC is not involved in the phonological or semantic aspects of language processing. This finding is consistent with a previous fMRI study showing that the left PITC is not activated during these two tasks (Nakamura et al., 2000).

When copying kana and kanji, the RTs and RA% scores were unaffected by rTMS over the left PITC. This finding is in good agreement with those of the lesion and cortical electrical stimulation studies of this region, which report that copying kana and kanji is not impaired (Soma et al., 1989; Usui et al., 2003). Because Japanese subjects can write kanji characters quite automatically through repeated practice, such visual kanji images may be important for activating the stored graphic motor patterns required for writing. Thus, the orthographic representation of kanji includes the graphomotor representation as well as the visual representation. It is possible that the grapheomotor representations for writing kanji and kana are stored in the frontoparietal network, in which lesions most commonly affect the writing of both forms of script (Iwata, 1984; Nakamura and Kouider, 2003).

Similarly, our findings showed that the left PITC is not associated with the grapheomotor aspects of writing.

In the mental recall of kanji and the kana-to-kanji transcription tasks, rTMS over a site 2 cm away (dorsal) from the left PITC had no effects on the RTs or RA% scores. Thus, the retrieval of the visual graphic form when writing kanji seems to be a function specifically confined to the PITC.

Because effects of rTMS spread trans-synaptically distant regions, spatial resolution becomes lower than the maximum resolution of single-pulse or paired-pulse TMS. Mapping studies within the motor or visual cortex using single-pulse TMS have reported a spatial resolution of 0.5–1 cm at the scalp surface, but, if using a prolonged train of rTMS, the spread of the effects along both corticocortical and cortico-subcortical connections may well lead to less focal effects (Pascual-Leone et al., 1994; Jahanshahi and Rothwell, 2000; Walsh and Cowey, 2000). Furthermore, several recent studies combining TMS with neuroimaging methods have demonstrated that TMS can produce, in addition to local effects on the directly targeted cortex, transsynaptic effects on distant cortical regions (Lee et al., 2003; Rounis et al., 2005; Valero-Cabre et al., 2005). In the present study, rTMS over a site 2 cm away from the left PITC and sham stimulation had no effects on the task performance. However, it remains possible that not only the PITC but also through PITC-specific connected brain regions participate in the task related to the retrieval of the visual graphic representation of kanji because of the methodological limitation of rTMS.

For experiments 2 and 3, some subjects performed the same task as the one they had done in experiment 1. However, because they participated in experiments 2 and 3 at least 1 month apart from experiment 1, we do not think that the learning effect might make a difference in task performance. Furthermore, we evaluated the change in task performance during baseline conditions (pre-rTMS) between experiments 1 and 2 or between experiments 1 and 3 for both RTs and RA% and found no significant difference. Thus, the variability of the task performance across subject groups was likely to be negligible in this study.

Functional role of the left PITC in tasks other than kanji writing

The left PITC, mainly corresponding to Brodmann area 37, constitutes part of the ventral visual pathway involved in the analysis of complex figures and object recognition (Sergent et al., 1992; Moscovitch et al., 1995; Clark et al., 1996; Price et al., 1996; Rosier et al., 1997; Ishai et al., 1999; Stewart et al., 2001; Rossion et al., 2003). In fact, patients suffering from alexia with agraphia of kanji caused by this lesion show only mild naming difficulties (Sakurai et al., 1994). However, our results do not imply that kanji are just complex figures and that Japanese people write kanji as they would draw objects, because kanji characters are strongly associated with semantics and phonology, which are implicitly activated on visual presentation of kanji, as well as visual graphic forms (Thuy et al., 2004). Therefore, the visual recognition of kanji is likely to use a different processing system from that of object recognition, although a similar brain region might be involved in both forms of processing.

Recently, some authors have referred to the left PITC as the "visual word form area" of the brain, although it is still controversial as to whether or not there is a confined area dedicated to word recognition (Cohen et al., 2002). This area is activated whenever subjects read or write printed words, and its function may be to encode the orthographic regularities of the writing system (Cohen et al., 2002; McCandliss et al., 2003). For example,

the regional differences from the caudal to the more rostral part of the left PITC corresponds to the predisposed perceptual gradient from global to local processing (Ito et al., 1995; Lerner et al., 2001). Moreover, a recent fMRI study reported that, in Japanese adults, this region was selectively activated under a condition requiring new linkages between unfamiliar letters and speech sounds, indicating that this region shows dynamic functional plasticity even in adults (Hashimoto and Sakai, 2004). Thus, the left PITC might be involved in the visual word recognition that is a necessary subprocess of writing kanji by tuning into its orthographic regularities.

Functional role of the right PITC

In the mental recall of kanji orthography and during kana-to-kanji transcription tasks, we found significantly shorter RTs after rTMS over the right (nondominant) PITC, whereas sham stimulation had no effect on RTs. Previous fMRI and magnetoencephalography studies have demonstrated weak activation or responses in the right PITC in some linguistic tasks, although this activation is much stronger on the left side (Nakamura et al., 2000; Cohen et al., 2002; Rossion et al., 2003). This strongly lateralized PITC activation may partially derive from the different functional importance of each hemisphere for language functions, including visual word recognition. A question then arises as to the nature of the functional role the right PITC might play in the processing of kanji.

In general, regarding the interhemispheric relationship in the language processing system, the dominant and nondominant hemispheres may work cooperatively or reciprocally suppress each other. There are two possible mechanisms by which the right PITC may contribute to kanji writing. One is that the right PITC plays a supplementary role to that of the left PITC, a hypothesis supported by tests on recovering aphasics and TMS studies (Basso et al., 1989; Knecht et al., 2002). The other is that the right PITC suppresses the function of the left PITC reciprocally based on the idea that the two hemispheres are equipotential for language functions at birth and that the language centers of one hemisphere become dominant by inhibiting homotopic areas in the other hemisphere via the corpus callosum during language acquisition (Netz et al., 1995; Karbe et al., 1998; Heiss et al., 2003). Based on the neural network model, Kinsbourne (2000) proposed that the two cerebral hemispheres are functionally equilibrate and reciprocally inhibit the areas that anchor them via corpus callosum (Kinsbourne, 2000). However, because lesion studies describing the effects of damage to the right hemisphere, including the PITC, are rare, the functional role of the right hemisphere remains unclear.

Recently, it has been reported that low-frequency rTMS is able to improve hemispatial neglect and nonfluent aphasia by the transient functional disruption of the corresponding area in the unaffected hemisphere, a phenomenon provisionally called paradoxical functional facilitation (Oliveri et al., 1999; Brighina et al., 2003; Martin et al., 2004). Moreover, other authors found similar paradoxical improvements in performances of hand movements or memory encoding after low-frequency rTMS over motor cortex or ventrolateral prefrontal cortex (Kobayashi et al., 2004; Kahn et al., 2005). A similar mechanism has been observed in animal models, in which a new lesion in the superior colliculus was shown to improve the visual dysfunction initially caused by an ipsilateral occipito-parietal lesion (Kapur, 1996; Lomber et al., 2002). The improvement of functional deficits by rTMS can be attributed to the normalization of the interhemispheric balance via the corpus callosum, through inhibiting the hyperactivation

of the unaffected hemisphere by releasing the reciprocal inhibition from the affected hemisphere (Theoret et al., 2003). Previous anatomical study showed the existence of the interhemispheric anatomical connections between the inferior temporal gyri (including the PITC) through the corpus callosum in monkeys (Demeter et al., 1990).

TMS can elicit facilitation effect on the targeted cortical region and enhance its normal function on some occasions. When studying the carryover effect of rTMS, frequency-dependent suppression or facilitation has been observed in various languages related to cortical regions as well as motor cortex. Low-frequency rTMS at 1 Hz over just anterior to Broca's area prolonged RTs for verb production (Shapiro et al., 2001), whereas rTMS at 20 Hz over Wernicke's area reduced RTs in a picture-naming task (Mottaghy et al., 1999). Moreover, the event-related TMS caused reduction of RTs in object naming or syntactic decision tasks when TMS was administered to Wernicke's or Broca's area at a specific timing (Topper et al., 1998; Sakai et al., 2002). To our knowledge, there are no evidences for inducing facilitation effect on the targeted region by low-frequency rTMS (<1 Hz), except for a certain type of preconditioning enhancing the plasticity. For example, after the cathodal direct current stimulation for 10 min to the primary motor cortex, rTMS at 1 Hz can increase the corticospinal excitability (Siebner et al., 2004). However, these techniques are different from that used in the present study. Therefore, it is not likely that low-frequency rTMS over the non-dominant PITC may directly facilitate its function.

Our results showing reduced RTs by transient disruption of the right PITC only in the tasks that require the visualization of kanji indicates that the functional suppressive action of the non-dominant PITC might be relevant to the improved retrieval of kanji orthography. The right PITC might be functioning to tune into the orthographic regularities of kanji by inhibiting the left PITC when retrieving a complex mental image of the kanji configuration. It should be noted, however, that the interhemispheric language processing system might vary between the different regions and/or language functions.

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