mobile phones for thirty minutes. The motor cortical output neurons are large, projection neurons of the motor cortex which are usually relatively resistant to metabolic stresses or adverse effects [Minckler, 1968; Brierley and Graham, 1984]. Therefore, it is not surprising that they were not affected by EMF exposure in normal subjects. On the contrary, small interneurons are susceptible to metabolic stress, such as hypoxia. The present results also indicated that the function of such small neurons of the motor cortex (GABAergic interneurons) was not impaired. This suggests that EMF emitted by mobile phones does not exert short-term adverse effects even on the sensitive structures of the motor cortex in normal subjects. As a whole, we could not detect any effects from 30 min of mobile phone exposure on the human motor cortex of normal subjects.

Another conspicuous finding of the present study is that in two patients with MS, the corticospinal tracts were not affected by the EMF emitted by mobile phones even though conduction block affected them after taking a bath. The hot bath effect is considered to be due to temperature dependent sodium channel dysfunction [Matthews et al., 1979; Bajada et al., 1980]. The ideal core temperature (temperature near to the brain) for humans is around 37 °C. This temperature is kept constant even though skin temperature is moderately changed by several factors of atmosphere around the subjects. Thus, when we take a bath at 42 °C for 30 min, the core temperature will increase only by a few tenths of a degree centigrade whereas, the skin temperature may approach 42 °C. The temperature rise of a few tenths of a degree induces no functional changes in normal subjects but causes conduction block in some patients with MS. This must be the mechanism for the hot bath effect. For the first time, we demonstrated conduction block at the intracranial corticospinal tracts after a bath in patients with MS. This confirms the idea that so-called hot bath effect is produced by conduction block. The finding that no significant changes were elicited in MEPs by EMF exposure leads to two important conclusions. (1) The EMF emitted by mobile phones does not increase the core temperature to the level of taking a bath. (2) The EMF exposure from mobile phones has no non-thermal adverse effects on axons at MS plaques.

Our present results are consistent with our previous results that neither auditory evoked potentials, sensory evoked potentials nor reaction times were affected by a mobile phone [Arai et al., 2003; Yuasa et al., 2006; Terao et al., 2006]. Even though we studied only two aspects of the human motor systems using available physiological methods, our results indicate that we can not detect any short-term effects on the human central motor systems from 30 min of EMF exposure from mobile phones in normal subjects as well as two patients with MS. However, there are several points to be considered before we make a firm conclusion on the effects of mobile phones on the human motor cortex. Our small sample size may not be enough to detect some subtle effects because of weak statistical power. We should therefore apply the same experiments to a large number of subjects before making a firm conclusion. In addition, the present study only addressed short-term effects. Since long-term effects may also be a side effect of mobile phones, future studies should be conducted with a design capable of addressing such effects.

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Modifying the Cortical Processing for Motor Preparation by Repetitive Transcranial Magnetic Stimulation

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Abstract

■ To investigate the effects of repetitive transcranial magnetic stimulation (rTMS) on the central processing of motor preparation, we had subjects perform a precued-choice reaction time (RT) task. They had to press one of two buttons as quickly as possible after a go signal specifying both the hand to be used and the button to press. A precue preceding this signal conveyed full, partial, or no advance information (hand and/or button), such that RT shortened with increasing amount of information. We applied 1200 to 2400 pulses of 1-Hz rTMS over various cortical areas and compared the subjects' performances at various times before and after this intervention. rTMS delayed RT at two distinct phases after stimulation, one within 10 min and another with a peak at 20 to 30 min and lasting for 60 to 90 min, with no significant effects on error rates or movement time. The effect was significantly larger on left- than on right-hand responses. RT was prominently delayed over the premotor and motor cortices with similar effects across different conditions of advance information, suggesting that preparatory processes relatively close to the formation of motor output were influenced by rTMS. In contrast, the effect of rTMS over the supplementary motor area and the anterior parietal cortex varied with the amount of advance information, indicating specific roles played by these areas in integrating target and effector information. The primary motor area, especially of the left hemisphere, may take over this processing, implementing motor output based on the information processed in other areas. ■

INTRODUCTION

Can we modify motor behavior noninvasively, and how? The question, frequently posed in the clinical setting, led repetitive transcranial magnetic stimulation (rTMS) to emerge as one of the potential tools for treating patients with movement disorders (Lefaucheur, 2005; Okabe, Ugawa, Kanazawa, & Effectiveness of rTMS on Parkinson's Disease Study Group, 2003; Siebner et al., 1999). Because it exerts a lasting effect on the stimulated cortical region or regions connected to it even after the stimulus pulses have ceased (Pascual-Leone et al., 1998), rTMS is expected to induce a lasting effect also on motor behavior. Studies conducted at the behavioral level are crucial if it is to be applied for clinical purposes; what is lacking in this field is the link between cause and necessity (i.e., between the changes in motor behavior and those in neural activity), such as those reflected in the lasting changes of motor cortical or sensory cortical excitability (Münchau, Bloem, Irlbacher, Trimble, & Rothwell, 2002; Civardi, Cantello, Asselman, & Rothwell, 2001; Enomoto et al. 2001; Gerschlager, Sibner, & Rothwell, 2001) or regional cerebral blood flow (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004, 2005; Hayashi et al., 2004; Okabe, Hanajima, et al., 2003).

Several studies to date have attempted to modify motor behavior by rTMS, and some reported a delay in reaction time (RT) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Schlaghecken, Münchau, Bloem, Rothwell, & Eimer, 2003) or a slowing of fast finger-tapping speed (Jäncke, Steinmetz, Benilow, & Ziemann, 2004), whereas others have failed to produce any significant effect (Kim, Park, Ko, Jang, & Lee, 2004; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Chen et al., 1997). Furthermore, the reported effects persist only up to 10 to 15 min after stimulation and disappear by 30 min, precluding clinical application. Instead of affecting the motor output directly, here we set out to modify motor behavior through the change in the motor preparation process using low-frequency (1-Hz) rTMS.

Many studies assume facilitatory effects of high-frequency rTMS and inhibitory effects of low-frequency rTMS below 1 Hz (Pascual-Leone et al., 1998; Chen et al., 1997). Despite some interindividual variability (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000), there is accumulating

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evidence that low-frequency rTMS can also suppress the excitability of cortical areas other than the motor cortex, including the visual cortex (Boroojerdi, Prager, Muellbacher, & Cohen, 2000), sensory cortex (Enomoto et al., 2001), and the prefrontal cortex (Robertson, Tormos, Maeda, & Pascual-Leone, 2001). In this study, we expected a similar inhibitory effect of rTMS on task performance, that is, to disrupt the normal processing of the stimulated areas.

Motor preparation is typically studied with an RT paradigm, in which a preparatory stimulus that fully or partially informs the subjects about the movement is followed by a delay period and, subsequently, by a response stimulus that signals the initiation of the movement. The function of the precue is to provide advance information about the movement to be performed and to allow the subjects to prepare some part of the forthcoming movement (Adam et al., 2003; Deiber, Ibanez, Sadato, & Hallett, 1996; Rosenbaum, 1980), causing a shortening of RT. Requin, Brener, and Ring (1991) dissociated two types of motor preparation: "event" versus "time" preparation. Because any motor task requires both a nonspecific motor readiness and a specific preparation process to be performed, the latter process of specific motor preparation should be controlled by designs that differ only in the preparatory phase before movements (Deiber et al., 1996). To study such "event preparation," we employed a precued variant of choice RT task (Goodman & Kelso, 1980; Rosenbaum, 1980) in which the precue provided complete, partial, or no information about the forthcoming movement and the RT to the go signal shortens with increasing amount of advance information, that is, depending on the degree of motor preparation (Possamaï, Burle, Osma, & Hasbroucq, 2002).

With this paradigm, various cortical regions have been shown to participate in motor preparation, such as the parietal, premotor, primary motor, and prefrontal cortices and the supplementary motor area (SMA) of both hemispheres (Connolly, Goodale, Cant, & Munoz, 2007; Naranjo et al., 2007; Verleger, Kotter, Jaskowski, Sprenger, & Siebner, 2006; Adam et al., 2003; Grammont & Riehle, 1999; Deiber et al., 1996; Requin et al., 1991; Requin, Lecas, & Vitton, 1990). Constituting a common anatomical substrate for motor preparation, these cortical regions are recruited to different degrees depending on the movement context. The present investigation aimed to differentiate functions of various areas in this network. By focally targeting each of the cortical regions with rTMS, we would obtain a different pattern of change in motor preparation. We were particularly interested in finding a region over which the effect of rTMS differs with the amount of advance information, because such an area should be primarily involved in the specific process of motor preparation.

We addressed whether rTMS exerts a lasting modulation on the cortical processing for motor preparation. Three questions were asked: How long would the rTMS effect, if present, last after the stimulation? Where would be the most effective site of stimulation for inducing this modulation and would there be a hemispheric lateralization for this effect? How would the effect vary with the amount of advance information, that is, depending on the degree of motor preparation? We show that rTMS exerts a biphasic modulation on the cortical stimulation, lasting for up to 60 to 90 min. The patterns of rTMS effect over various cortical areas and its variation with advance information given by the precue provided further insights into the cortical network for motor preparation.

METHODS

Subjects

A total of 13 right-handed normal male subjects participated in this study after giving written informed consent. All subjects were consistent right-handers with an Edinburgh Handedness Inventory score of 100 (Oldfield, 1971). The experimental procedures conformed to the Declaration of Helsinki and were approved by the Ethical Committee of the University of Tokyo.

Experimental Setup and Task Procedure

To study the process of motor preparation, we made the subjects perform a variant of precued-choice RT task with four response alternatives as employed in our previous study (Figure 1A) (Terao et al., 2005; Hoshi & Tanji, 2000; Goodman & Kelso, 1980; Rosenbaum, 1980). The subjects had to press one of two buttons with the left or right hand as quickly as possible as specified by the go signal. A precue preceding this by a period randomized between 2 and 3 sec conveyed full, partial, or no advance information (hand and/or button) about the signal.

There were four precue information conditions. In the full-information condition, the precue identical to the go signal specified both the button to be pressed and the hand to be used. In the partial-hand (PH) condition, the precue allowed prespecification of the hand but not the button. In the partial-button (PB) condition, the precue provided information about the button but not about the hand. In the no-information condition, no advance information was provided. If the participants made use of the advance information, RT would shorten with increasing amount of information.

The visual stimuli for the go signal (see below) were generated by Superlab Pro version 2 (Cedrus, San Pedro, CA) and presented on a white background of a 17-in. monitor screen (Mutiscan 17sf9; Sony, Tokyo, Japan), subtending a visual angle of approximately 5.9° × 10.9° at a viewing distance of 50 cm. A response pad (RB-620; Cedrus) was furnished with two home keys and two target buttons.

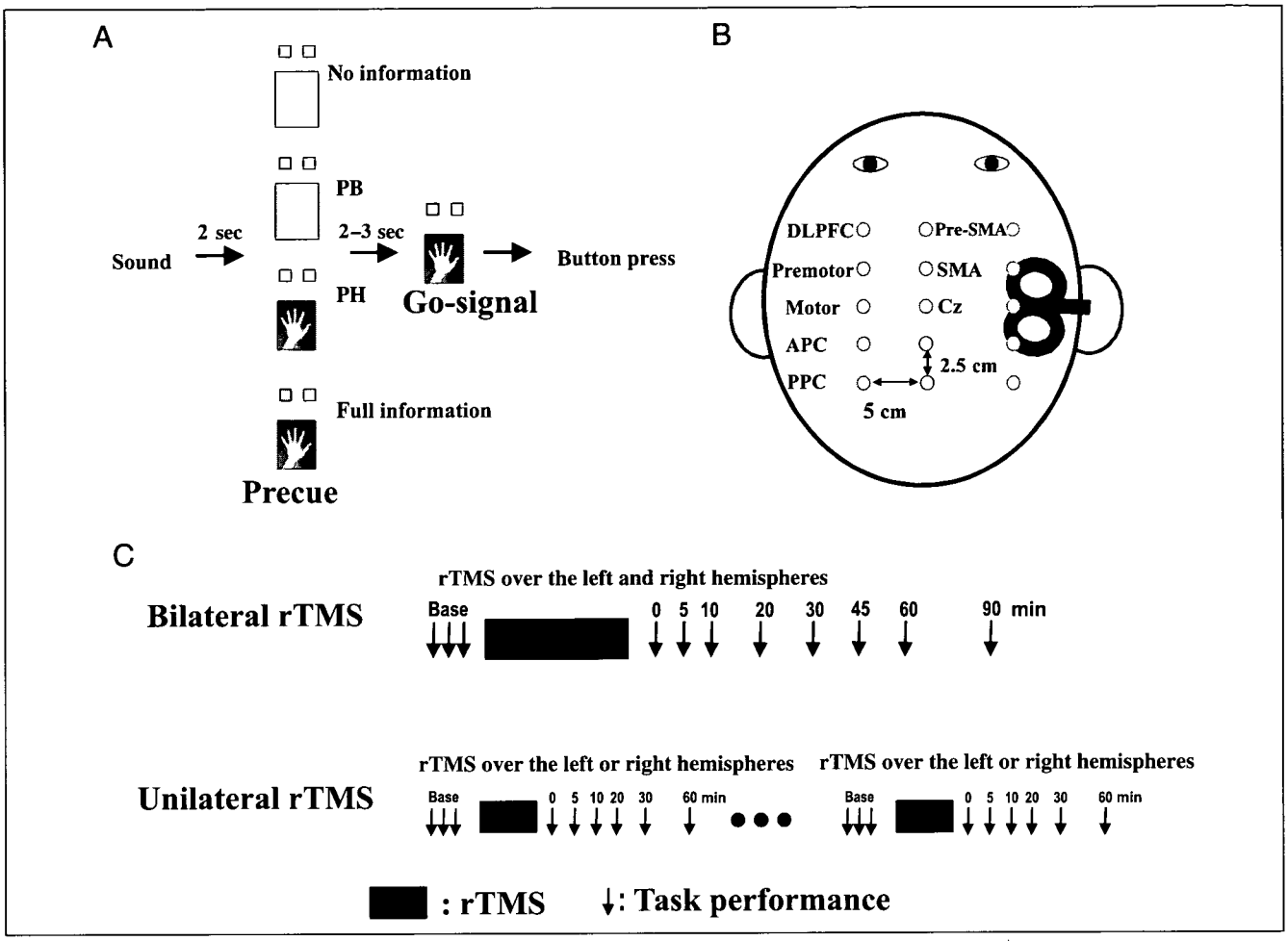

Figure 1. Task procedure and sites of TMS. (A) Task procedure. A beep sound signaled the beginning of each trial. Two seconds later, a precue was presented on the monitor screen for 500 msec, which provided the subjects with no information about the button to be pressed (no-information condition), partial information about either the button to be pressed (PB condition) or the hand to be used for pressing (PH condition), or information about both the button and hand (full-information condition). After a random interval of 2 to 3 sec, the go signal prompted the subjects to release the home key with one of the hands and press the indicated target button (gray square) with the same hand. (B) Sites of TMS. Thirteen scalp positions were selected for stimulation, either over the midline or over lines 5 cm to the left or right of it. The distances between these grid points were 2.5 cm in the anteroposterior direction. The lateral scalp positions were considered to represent the DLPFC, premotor and motor cortices, APC, and PPC regions. The medial scalp positions included Cz and points 2.5 and 5.0 cm anterior to it, which were presumed to lie over the SMA and pre-SMA, respectively. (C) (Top) bilateral TMS. In Experiment 1, stimulation was given bilaterally, with 1200 pulses of 1-Hz rTMS delivered successively over one hemisphere and then over the homologous region of the other hemisphere or 2400 pulses in total over the medial cortical areas. The task performance was followed up at various time intervals before and after this intervention. Downward arrows represent times of task performance. (Bottom) unilateral TMS. In Experiment 2, the effect of rTMS over the premotor and motor cortices was studied separately for each hemisphere. The task performance was followed up at various periods before and after stimulation of one hemisphere (1 Hz, 1200 pulses), which was repeated for the other hemisphere. In Experiment 3, the stimulation was performed unilaterally over the premotor and motor cortices as well as over the SMA but with the same stimulation parameter (1 Hz, 1200 pulses). Base = prestimulation baseline.

The subjects were comfortably seated in a chair and instructed to keep pressing the home keys of the response pad with the index fingers of both hands until the go signal was presented. On its presentation, the subjects quickly released the home key with the indicated hand (left or right) and pressed the left or right target button of the response pad with the index finger of the same hand (Figure 1A). A precue preceding the go signal by 2 to 3 sec was presented that conveyed full, partial, or no information about the movement parameters (i.e., the hand [right or left] and the button to be pressed [right or left]). In the full-information condition, the precue identical to the go signal was presented, which specified both the button to be pressed and the hand to be used. In the PH condition, the upper picture in the cue indicating the button was left blank. In the PB condition, the lower picture in the cue indicating the hand was left blank. In the no-information condition, the upper two squares as well as the lower picture were all left blank. The precue was always valid, such that the information provided did not contradict information included in the go signal. Each block of the test session

comprised 32 trials (4 information conditions × 4 response alternatives × 2 replications for each trial type) that lasted for 6 to 7 min.

The RT was measured between the onset of the go signal to the release of the home key, and the movement time (MT) was defined as the time from the release of the home key to the pressing of target button. Errors refer to those in which the nonindicated hand left the home key regardless of whether the indicated finger moved or not (termed *selection errors*) and those in which the wrong button was pressed regardless of which home key was released (termed *response errors*).

Transcranial Magnetic Stimulation

Setup

TMS was delivered with a figure-eight coil (inner diameter = 8 cm; outer diameter = 11.5 cm) connected to a magnetic stimulator (Magstim Rapid; Magstim, Welwyn Garden City, UK), producing a biphasic pulse with a rise time of approximately 100 μsec and a maximal output of 1.6 T when connected to a figure-of-eight coil. We used this type of coil to study the topography of effective regions with maximal spatial resolution, approximately at 1 cm (Wilson, Thickbroom, & Mastaglia, 1993; Wassermann, McShane, Hallett, & Cohen, 1992).

The coil was fixed tangentially over the scalp by the hand of an experienced experimenter, inducing a posterior-to-anterior current in the brain. A clamping system was used to bear most of the weight of the TMS coil, but the exact position of the coil was adjusted with the hand of the experimenter. For this purpose, we marked the coil position over the scalp and made sure that the coil did not get displaced throughout the experiment. We first looked for the optimal scalp position ("hand motor area") over each hemisphere where the maximal motor evoked potential (MEP) could be elicited in contralateral first dorsal interossei muscles and then determined the active motor threshold over the hand motor area of the right hemisphere. To ensure physical stimulation of the brain structure and at the same time minimize current spread into regions other than the target area, the stimulus intensity was set at a value incremented by 5% of maximal stimulator output above this threshold, which ranged from 35% to 65% (mean ± standard error [*SE*] = 48.3 ± 3.3%) of the maximal output.

Stimulus Locations

For rTMS, we selected 13 scalp positions over the lateral and medial convexity, according to previous neuroimaging studies (see Discussion) and our previous single-pulse TMS study (Terao et al., 2005). Over the midline, the selected scalp positions were Cz (vertex) and positions 2.5 and 5 cm anterior to that point. Five points each were also marked over two lines 5 cm to the left and to the right of the midline. In all subjects, the middle point of these five points in the anteroposterior direction coincided with the hand motor area determined above (5–6 cm to the left and right of Cz) and the other points were 2.5 and 5 cm anterior and posterior to it. According to previous TMS and neuroimaging studies (Schluter, Rushworth, Passingham, & Mills, 1998), the lateral scalp regions corresponded to the dorsolateral prefrontal cortex (DLPFC), premotor, motor, and the anterior and posterior parietal cortices (APC and PPC, respectively). The two midline locations anterior to Cz corresponded to the pre-SMA and SMA (Figure 1B). The validity of stimulation sites was confirmed by a neuronavigator system (Navigated Brain Stimulation System eXimia NBS; Nexstim, Helsinki, Finland).

Stimulation Protocol

Experiment 1

Experiment 1 aimed to investigate the time course of rTMS aftereffect on the performance measures of the precued-choice RT task. It also aimed to find out regions where rTMS was effective in inducing a significant change in task performance. The subjects performed the task before and at several time points after rTMS (at 0, 5, 10, 20, 30, 45, 60, and 90 min). By comparing the task performance pre- and post-rTMS in terms of changes in RT, MT, and error rates, we studied how the aftereffect of rTMS varied with time, stimulation location, and precue information.

To maximize the aftereffect, rTMS of the lateral convexity was applied bilaterally (Figure 1C, top: bilateral rTMS). A total of 1200 pulses of 1 Hz TMS each were given to homologous cortical regions of both hemispheres successively, for example, 1200 pulses of 1 Hz TMS were given to the premotor cortex of the right hemisphere and then to the same area of the left hemisphere, or vice versa. As described in the Introduction, although 1-Hz TMS modulates many aspects of motor cortical excitability, no impairment of manual motor control has been demonstrated convincingly during simple motor tasks (see also Lee et al., 2003), presumably because of the ability of the brain to compensate for any damage or changes in function occurring in its local region. We, therefore, expected to obtain a greater effect if we stimulated both hemispheres successively. The order of rTMS sites was counterbalanced across the subjects. Furthermore, for each rTMS site, the order in which the left or right hemisphere was stimulated first was also counterbalanced among subjects. When stimulating the midline cortical regions, bilateral 2400 pulses of 1-Hz rTMS were given over each site to balance the load of stimuli with rTMS of the lateral convexity. At each stimulus location, the subjects performed three blocks of the task as baseline trials each time before receiving rTMS. After rTMS, we followed up

their performance at 0, 5, 10, 20, 30, 45, 60, and 90 min. Thus, the trial number for each subject amounted to a total of 352 trials (32 trials × 11 time points).

Placing the magnetic coil over the midline, cortical regions of both hemispheres adjacent to the coil may be stimulated at the same time because of their proximity to the coil, a situation not encountered when stimulating the lateral convexity. Therefore, dosages of rTMS over the medial and lateral convexity cannot be balanced reliably with any stimulation parameters, and direct comparisons between the medial and lateral rTMS are not tenable (see Discussion). It should be noted that the above stimulation protocol was selected to maximize the rTMS effect and find out the region where the rTMS effect is maximal over the medial cortical regions.

Only one site was studied per day. The time interval between two different sessions (i.e., different sites) was 1 to 3 weeks.

Experiment 2

In Experiment 1, we showed that the aftereffect of rTMS was maximal over the premotor and motor cortices (M1) over the lateral convexity. Here we studied the laterality of aftereffect over these areas by applying unilateral rTMS over the motor and premotor cortices of the left or right hemisphere.

rTMS was performed unilaterally; the subjects received 1200 pulses of 1-Hz rTMS over the motor or premotor cortex of one hemisphere (Figure 1C, bottom: unilateral rTMS). They performed the task before (baseline trials) and 0, 5, 10, 20, 30, and 60 min after rTMS. After a rest period of more than 2 hr (when the rTMS effect was expected to have already subsided), the subjects received another 1200 pulses of rTMS over the homologous region of the contralateral hemisphere. The subjects again performed the task before rTMS and were then followed up at the same time intervals after rTMS. The order in which the left or right hemisphere was stimulated first was randomized among subjects.

Experiment 3

In Experiment 1, midline cortical regions received 2400 pulses at each single location, whereas lateral cortical regions received 1200 pulses for each side. As stated above, this procedure was meant to balance the load of stimulation over both hemispheres. However, it is possible that the biphasic aftereffect of rTMS over the lateral convexity could have emerged from the very fact that the two hemispheres were stimulated one after another (see Discussion). Meanwhile, as mentioned above, we actually have no good reason that the dosages of rTMS over the medial and lateral convexity can be balanced reliably with the above stimulation parameters.

On the other hand, although we performed unilateral stimulation over the lateral convexity in Experiment 2, this experiment did not include a midline stimulation condition. Thus, the claim that rTMS over the SMA has selective effect on one type of cueing condition (full-information condition) but not over the premotor and motor cortices comes only from Experiment 1 where the confound exists.

To cope with these problems, we performed a follow-up experiment in which these three cortical regions (premotor and motor cortices of the left hemisphere as well as the SMA) were stimulated using the exact same stimulation parameters (1200 pulses at 1 Hz). The same 10 subjects who participated in the part of Experiment 1 addressing the effect of precue information on the performance measures were recruited for this experiment. In Experiment 3, we used only two precueing conditions (full- and no-information conditions) to increase the number of trials per condition; in Experiment 1, there were 8 trials per precue information in each block of session. In the follow-up experiment, the number of trials per condition was increased to 20.

Data Analysis and Statistical Assessment

Data from all 13 subjects were used for statistical analyses in baseline trials. Data from 6 subjects that received rTMS over all the sites were used to study the topography of rTMS effect in Experiments 1 and 2. To analyze the effect of precue information on task performance (Experiment 1) and also in Experiment 2, data from 10 of 13 subjects who underwent rTMS sessions over the premotor and motor cortices, the APC, and the SMA were used. The subjects recruited in all the experiments were well trained in the task and were ascertained to show a very stable performance across time despite fatigue, because they participated in our previous study (Terao et al., 2005). The error rate of task performance of these subjects was less than 10% of the trials, and the number of time error (see below) was less than 5% of the trials.

Trials with no responses made within 3 sec after the go signal, with RT less than 100 msec or exceeding 900 msec (time error), and with premature responses before the go signal were also discarded before further analyses. Furthermore, for the RT and MT analyses, all trials with errors (selection and response errors) were excluded. Then, the mean values of each measure before (baseline) and at each time point after rTMS were computed for each subject. On the other hand, the error analysis focused on whether TMS changed the frequency of errors.

For descriptive purposes, we subtracted the baseline values (with the same subject, response hand and precue information) from the mean RT and MT for individual time points at each site and expressed these subtracted values as a ratio (percentage) of the baseline values (termed *RT* and *MT ratios*, respectively). We first obtained the mean ratios per subject and then computed the average ratio across all subjects. Ratios were

calculated for the selection and response error rates in a similar manner.

For statistical analyses in Experiment 1, each of the behavioral measures (RT, MT, selection, and response error rates) was subjected to a repeated measures analysis of variance (ANOVA) with the following factors: site (DLPFC, premotor, motor, APC, PPC, pre-SMA, SMA, and Cz), time after rTMS (0–5, 10, 20, 30, 45–60, and 90 min; time points of 0 and 5 min and those of 45 and 60 min were collapsed), response hand (left or right), and precue information condition (full, PH, PB, or no). We selected one to three factors of the five possible factors that were considered appropriate for analysis. First, to look for the cortical area over which a significant change in RT, MT, or the error rates was induced, repeated measures ANOVA with the factor time was carried out at each of the studied regions. Pooling the data for all the sites investigated, the focality of the rTMS effect was analyzed with a two-way ANOVA with factors site of rTMS and time. Subsequently, the effect of rTMS on left- and right-hand responses was analyzed by adding the factor hand. To address how the rTMS aftereffect varied with precue information, we entered the RT data averaged across all the time points at each site into a two-way ANOVA with factors precue information and stimulus location. ANOVA was carried out for MT, and selection and response error rates in a similar way.

For Experiment 2, the performance measures were entered into repeated measures ANOVA with the following factors: site (premotor or motor cortex), hemisphere stimulated (left or right), time after rTMS (0, 5, 10, 20, 30, and 60 min), and response hand (left or right). For Experiment 3, the factors were site (premotor or motor cortex or SMA), time after rTMS (0, 5, 10, 20, 30, 45, and 60 min), and precue information (no or full).

For all the behavioral analyses, the significance criterion was set at $p < .05$. Contingent on the significance of analyzed effects and interactions, a post hoc analysis using Bonferroni/Dunn's correction for multiple comparisons was carried out to see what differences contributed to the significant differences detected by ANOVA.

RESULTS

Performance in Baseline Trials

Reaction Time

Across the 13 subjects recruited for baseline trials, RT decreased with an increasing amount of precue information as expected [effect of precue information: $F(3,36) = 675.479, p < .0001$] (Table 1). Overall, RT was comparable for the left and right hands [effect of hand: $F(1,12) = 0.242$, $p = .623$], but the interaction between precue information and hand reached significance [$F(3,36) = 8.587, p < .0001$]. This reflected RT being slightly shorter for the left hand than for the right in the more informative (full and PH precue) conditions ($p < .0009$, corrected for multiple comparisons) but comparable for both hands in the less informative (PB and no-precue) conditions ($p > .05$). The same trend was noted for the 6 subjects recruited for Experiments 1 and 2 [effect of precue information: $F(3,15) = 570.71, p < .0001$; effect of hand: $F(1,5) = 0.016, p = .8993$; interaction between precue information and hand: $F(3,15) = 7.689$, $p < .0001$] and for the 10 subjects recruited for the part of Experiment 1 addressing the effect of precue information on task performance and also in Experiment 3 [effect of precue information: $F(3,27) = 540.41$, $p < .0001$; effect of hand: $F(1,9) = 0.735, p = .39$; interaction between precue information and hand: $F(3,27) = 8.828$, $p < .0001$].

Movement Time

The MT was 174.4 ± 18.2 msec on average and was slightly but significantly longer in the full-information and PH conditions than in the other two precue conditions ($p < .05$ after Bonferroni's correction; there was a similar trend for the 6 subjects in Experiments 1 and 2, $p < .0001$, and the 10 subjects in Experiment 3, $p = .082$; Table 1). MT was similar for the left and right hands across all the information conditions [effect of hand: $F(1,12) = 0.46$, $p = .51$; for the 6 subjects in Experiments 1 and 2: $F(1,5) = 0.25$, $p = .64$; for the 10 subjects in Experiment 3: $F(1,9) = 2.11$, $p = .18$].

Table 1. Baseline Task Performance: RT and MT

	No	*PB*	*PH*	*Full*	*Total*
RT (msec)					
Left hand	539.6 ± 21.6	517.5 ± 14.4	441.1 ± 12.6	370.4 ± 14.1	475.5 ± 8.2
Right hand	523.6 ± 16.3	515.5 ± 13.0	449.1 ± 7.7	388.8 ± 14.6	474.0 ± 7.1
MT (msec)					
Left hand	172.7 ± 19.6	173.4 ± 18.7	175.5 ± 19.6	177.0 ± 18.9	174.7 ± 19.1
Right hand	172.9 ± 18.1	170.9 ± 16.6	175.9 ± 17.6	176.2 ± 17.5	174.0 ± 17.3

Selection Error Rate

Overall, the subjects released the wrong side of the home key in 2.1 ± 0.5% (mean ± *SE*) of the baseline trials before rTMS. The selection error rate was significantly smaller for the full and PH than for the PB and no-information conditions (no-information and PB conditions > PH and full-information conditions: $p < .05$, corrected for multiple comparisons, also for the 6 subjects in Experiments 1 and 2 and the 10 subjects in Experiment 3; Table 2). Selection error rates of the left and right hands were similar [effect of hand: $F(1,12) = 0.70$, $p = .42$; for the 6 subjects in Experiment 1: $F(1,5) = 0.017$, $p = .90$; for the 10 subjects in Experiment 3: $F(1,9) = 2.22$, $p = .17$].

Response Error Rate

The subjects pressed the wrong target button in 5.4 ± 0.9% of the baseline trials. The error rate was slightly smaller under the PH and full-information conditions than under the PB and no-information conditions ($p < .0001$, also for the 6 subjects in Experiments 1 and 2 as well as for the 10 subjects in Experiment 3; Table 2). Overall, the error rate was slightly larger for left-hand responses (5.8 ± 1.0%) than for right-hand responses (4.9 ± 0.8%), although the difference between the hands failed to reach significance [effect of hand: $F(1,12) = 0.067$, $p = .80$; for the 6 subjects in Experiment 1: $F(1,5) = 2.30$, $p = .19$; for the 10 subjects in Experiment 3: $F(1,9) = 1.38$, $p = .27$].

Experiment 1: Time Course and Topography of rTMS Aftereffect

rTMS Effect on RT

Biphasic time course of the rTMS aftereffect. To look at the time course of rTMS aftereffect at each site, we averaged the RT delay relative to baseline induced by rTMS across the four precue conditions at each time point. Figure 2 shows the averaged time courses of the RT delay followed up at various time points after rTMS was applied over different areas, both for the delay of RT in milliseconds (Figure 2A) and for the delay of RT expressed in percentage of the baseline RT (Figure 2B). We noted two phases of significant RT delay as indicated by asterisks. The first of these had a peak within 0 to 5 min after rTMS and lasted up to 10 min; the second reached a peak within 20 to 30 min and lasted for 60 min after stimulation. At 90 min after rTMS, RT had returned to the baseline level (difference from baseline performance: $p > .05$) and will not be considered in the following analyses.

Notably, 10 min after rTMS (i.e., at an interval just between the two peaks), no significant delay of RT was observed over any studied region ($p > .05$). Furthermore, the induced delay at 10 min was different from 0 to 5 min ($p = .033$) as well as from 20 to 30 min after rTMS ($p < .0002$), which confirmed that there were two distinct phases of the rTMS aftereffect.

Furthermore, the biphasic modulation was noted also for the data pooled across all the effective brain regions (motor, premotor, APC, SMA, and Cz), suggesting that the modulation was common to all of the effective sites (Figure 3). Again, plots are shown for the delay of RT in milliseconds (Figure 3A) and for the delay of RT expressed in percentage of the baseline RT (Figure 3B). Again, these figures show two significant peaks with the nonsignificant time interval at 10 min in between.

Topography of TMS effect on RT. To look for the cortical regions effective in inducing a behavioral effect, we calculated the mean value of RT delay across the entire time points after rTMS and took this as an overall index of the effect of rTMS at that site. Figure 4A plots, for the average of all subjects, the delay of RT in milliseconds against the site of stimulation. Over the lateral cortical regions, rTMS induced the most prominent delay when applied to the premotor cortex. A smaller RT delay was also induced over the motor cortex and APC, whereas the delay induced over the DLPFC and PPC was minimal. Over the midline cortical regions, the RT delay was maximal when rTMS was applied over the SMA, but the delay was smaller with rTMS over the pre-SMA and Cz. A similar topography

Table 2. Baseline Task Performance: Selection and Response Error Rates

	No	*PB*	*PH*	*Full*	*Total*
Selection error rate (%)					
Left hand	3.2 ± 0.7	3.5 ± 0.9	0.4 ± 0.6	0.2 ± 0.6	1.9 ± 0.5
Right hand	4.1 ± 1.3	3.9 ± 1.2	0.3 ± 0.1	0.7 ± 0.3	2.2 ± 0.4
Response error rate (%)					
Left hand	8.2 ± 1.3	6.4 ± 1.1	5.3 ± 1.0	3.5 ± 0.7	5.8 ± 1.0
Right hand	6.1 ± 1.1	6.0 ± 1.1	4.0 ± 0.8	3.4 ± 0.6	4.9 ± 0.8

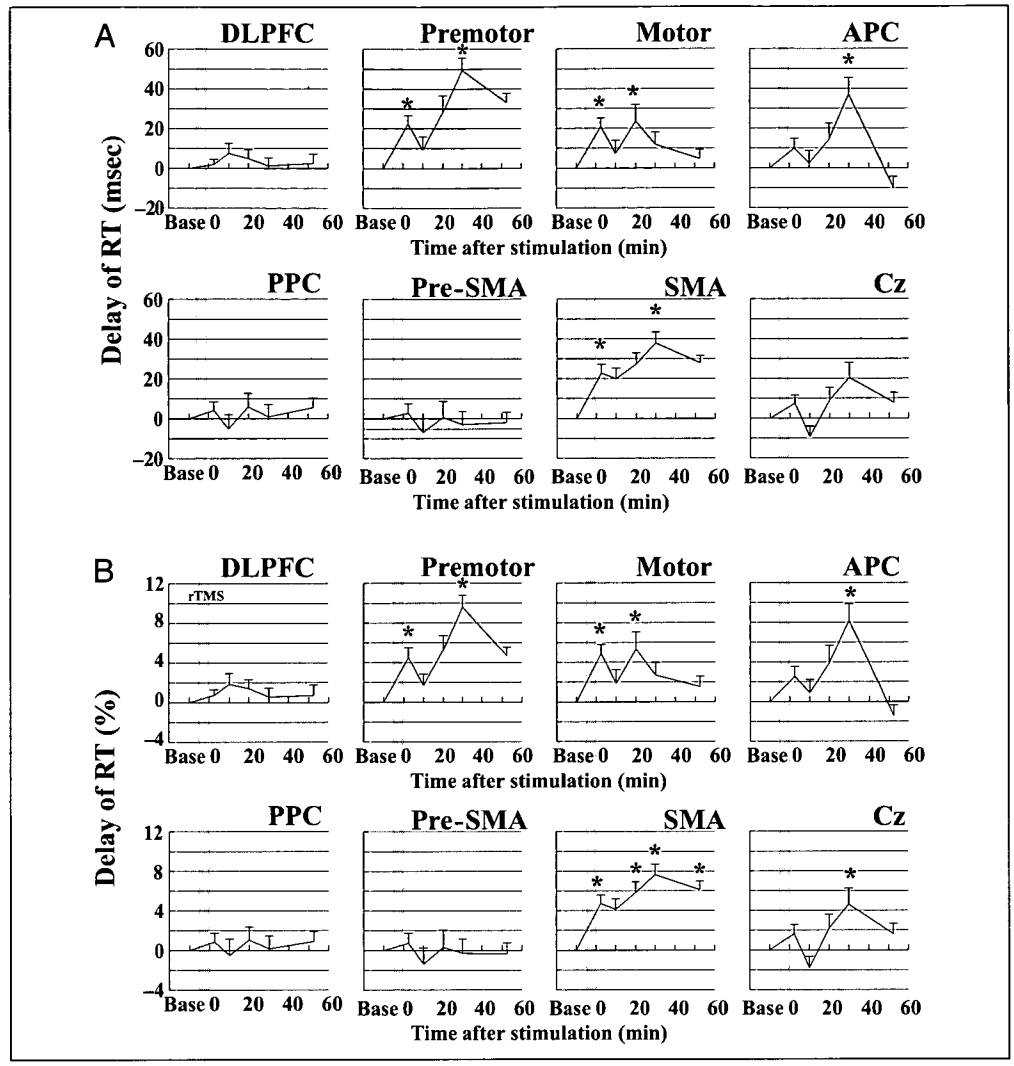

Figure 2. Time courses of the rTMS aftereffect over various cortical regions. The RT delay expressed in either (A) milliseconds or (B) percentage (RT ratio) was plotted as a function of the time after stimulation. The vertical gray bars in each plot denote the time of rTMS. Base = prestimulation baseline. *Significant difference from baseline level ($p < .05$, corrected for multiple comparisons). Error bars give *SE*s (also in the following figures).

of rTMS effect was also noted for the delay in RT expressed as a percentage of baseline RT (Figure 4B). Over the lateral convexity, rTMS induced a significant RT delay as compared with the baseline when applied over the premotor cortex as well as over the motor cortex and APC [effect of time: premotor cortex: $F(5,25) = 12.495$, $p < .0001$; motor cortex: $F(5,25) = 4.013$, $p = .013$; APC: $F(5,25) = 6.788, p < .0001$] but not over the DLPFC and PPC. Over the midline cortical regions, the delay induced by rTMS was largest over the SMA [i.e., significant relative to baseline performance; effect of time: $F(5,25) = 16.678, p < .0001$], smaller over Cz [$F(5,25) = 3.219, p = .0068$], but not significant over the pre-SMA ($p = .8767$). Therefore, the effective sites over the lateral convexity for inducing a delay were the premotor and motor cortices and the APC. Over the medial convexity, the most effective site was the SMA, followed by Cz.

Over the effective regions (premotor and motor cortices and APC over the lateral convexity and SMA and Cz over the midline), the aftereffect of rTMS on RT was significantly larger on left-hand responses than on the right [effect of response hand: $F(1,5) = 0.836, p = .0010$], although the baseline RTs were similar for both hands (Table 1). The greater effect on left-hand responses was common to all the effective stimulation sites [effect of hand: $F(1,5) = 11.231$, $p = .0008$; interaction between response hand and stimulus site: $F(4,20) = 0.609$, $p = .66$; Figure 5A]. Over the pre-SMA, the RT delay induced by rTMS was larger for right-hand responses than for the left.

Because there were two distinct phases in the rTMS aftereffect (see previous section), we collapsed the entire time points into two phases: the early phase corresponding to 0 to 10 min after rTMS and the late phase corresponding to the time points thereafter. The larger aftereffect on left-hand responses persisted throughout the early and late phases with rTMS over all the effective stimulation sites, except over APC during the early phase [time interval of TMS (early or late) × response hand: $F(1,5) = 3.180, p = .074$; site of stimulation × time interval of TMS (early or late) × response hand: $F(4,20) = 0.494$, $p = .74$; Figure 5B]. Again, over the pre-SMA, the

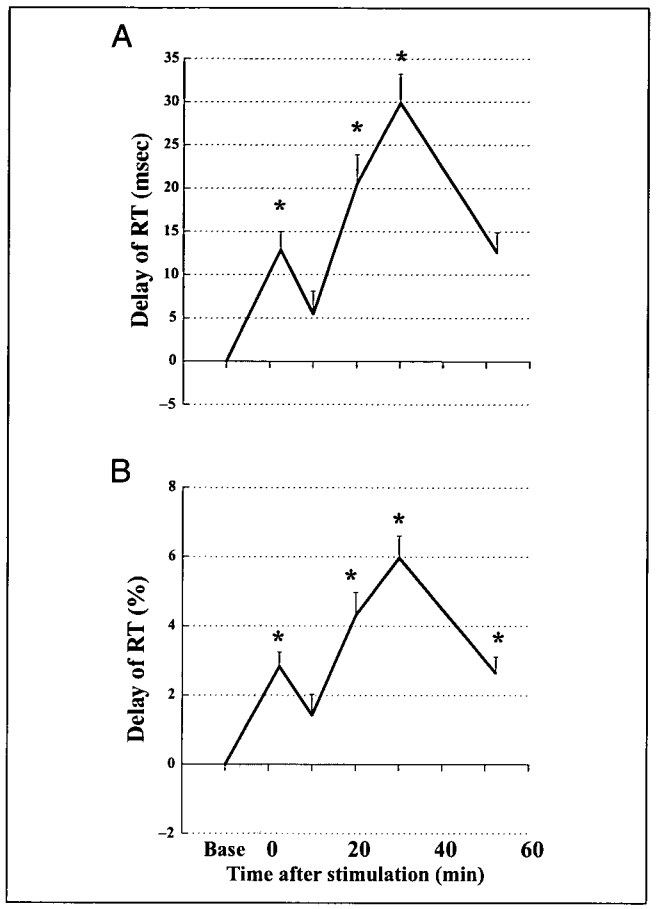

Figure 3. Time courses of the rTMS aftereffect for the data pooled across effective regions (premotor and motor cortices and APC over the lateral convexity and SMA and Cz over the midline). Plots are shown separately for the (A) raw RT delay data and (B) RT delay expressed as a percentage of baseline RT. Base = prestimulation baseline. Conventions as in Figure 2.

RT delay induced by rTMS was larger for the right-hand responses than for the left for both of these periods.

Precue information and distribution of the rTMS aftereffect. In 10 subjects, we now went on to investigate whether rTMS over different cortical regions affected the performance differently under different amounts of precue information. Here we focused on the most effective regions (i.e., motor and premotor cortices and APC over the lateral convexity and SMA over the midline) in a similar manner to that of Deiber et al. (1996). The three-way interaction among precue information, site of stimulation, and time after rTMS was insignificant [$F(45,405) = 0.846, p = .77$], suggesting that the impact of precue information and site of stimulation on RT was not affected by time. Thus, we averaged the RT data across all the time points but separately under different precue information conditions to study how the aftereffect varied with the precue information when rTMS was applied over different cortical regions (Figure 6).

Precue information significantly affected the rTMS aftereffect [effect of precue information: $F(3,27) = 5.703$, $p = .007$], with a greater effect noted for the full-information condition than for the other three conditions. Furthermore, the effect of precue information varied with the site of stimulation [interaction between precue information and site: $F(9,81) = 2.763, p = .032$], which indicated that rTMS had a site-specific effect on RT. Specifically, rTMS over the premotor and motor cortices resulted in a similar magnitude of RT delay irrespective of the precue information [effect of precue information: premotor cortex $F(3,27) = 1.067, p = .36$; motor cortex $F(3,27) = 0.369, p = .78$; Figure 6A, B]. In contrast, over the SMA, rTMS induced a significantly larger RT delay under the full-information condition than under the other three conditions [Figure 6C; effect of precue information: $F(3,27) = 3.925, p = .0084$; post hoc analysis demonstrated the following difference: full > no, PB, PH, $p < .011$]. Over the APC (Figure 6D), rTMS induced a significantly larger RT delay under the full-information and PH conditions in comparison with the other two conditions [effect of precue information: $F(3,27) = 8.286, p < .0001$; post hoc analysis revealed the following difference: full > no, full > PB, PH > PB, $p < .003$].

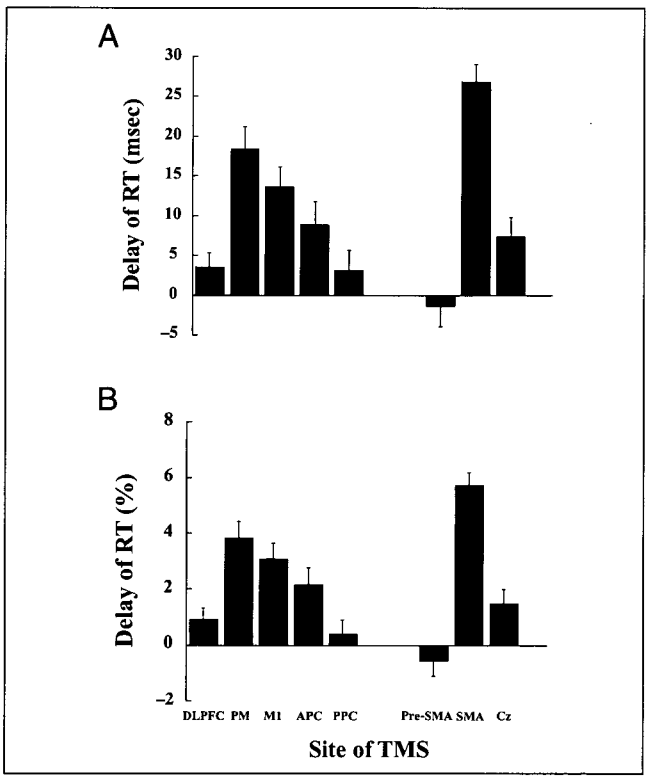

Figure 4. The topography of TMS effect on RT. The plots show the aftereffect averaged across all subjects when rTMS was applied over various cortical regions. The magnitude of aftereffect (i.e., RT delay) is given in (A) milliseconds and (B) percentages of corresponding baseline RTs (RT ratio). Plots are shown separately for the lateral (left) and medial (right) cortical regions.

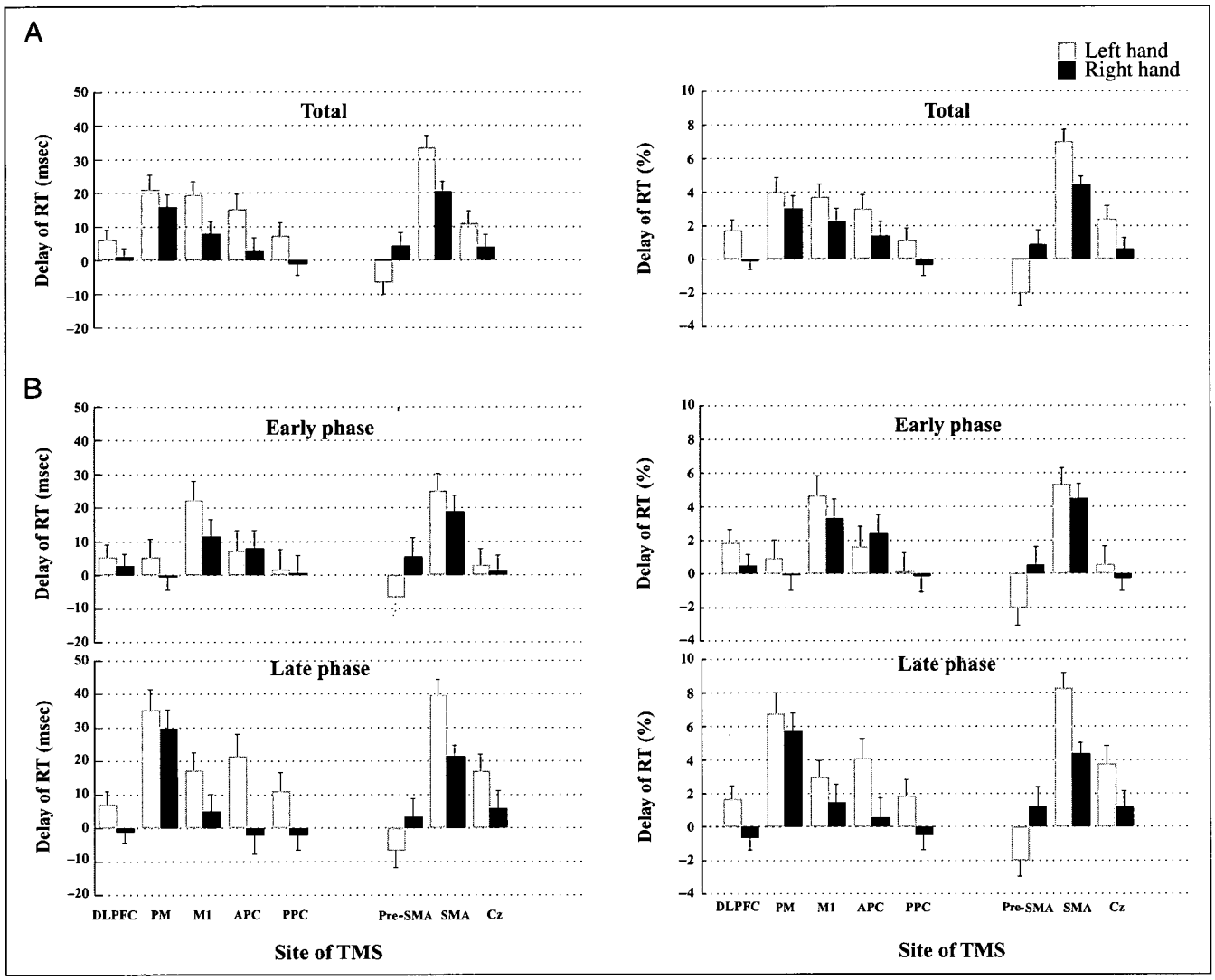

Figure 5. Comparison of aftereffects on left- and right-hand responses. The aftereffect was plotted as a function of the site of TMS but separately for left- and right-hand responses. The gray and black bars in each plot stand for left- and right-hand responses. RT ratios were averaged across the (A) entire periods studied or (B) separately for the early and late phases of the followed-up time interval.

rTMS Effect on Error Rates and MT

Error rate. The selection error rate was not affected by the time interval of stimulation, that is, no significant deviation in error rate from the baseline level was noted at any time point after rTMS, regardless of the site of stimulation ($p > .1$). Similarly, the response error rate did not deviate from the baseline level at any time interval after rTMS ($p > .09$) at any site of stimulation.

Movement time. When rTMS was applied over the lateral cortical regions, MT did not vary significantly with the time after rTMS [effect of time: $F(5,25) = 1.774, p = .145$] at any site of stimulation [interaction between time and stimulus site: $F(20,100) = 1.066, p = .38$]. Also, when rTMS was applied over the midline cortical regions, MT did not change significantly with time [effect of time: $F(5,25) = 0.157, p = .97$], although there was a slight interaction between time and stimulus site [$F(15,75) = 2.978, p = .047$]. Nevertheless, at each of the studied regions, MT did not deviate significantly from the baseline value at any time interval after stimulation ($p > .05$). This suggested that MT was not affected by rTMS, whereas the movement amplitude was controlled (the distance between the home keys and the response buttons was constant throughout the experiments), that is, the motor output in terms of MT and amplitude was not affected by rTMS.

Experiment 2: Laterality of the rTMS Aftereffect Over the Premotor and Motor Cortices

Over the premotor areas (Figure 7D), the effects of left- and right-hemisphere rTMS were comparable throughout the time points studied [effect of hemisphere stimulated: $F(1,5) = 0.070, p = .79$; interaction between time and hemisphere: $F(5,25) = 0.187, p = .97$]. The effect of hand

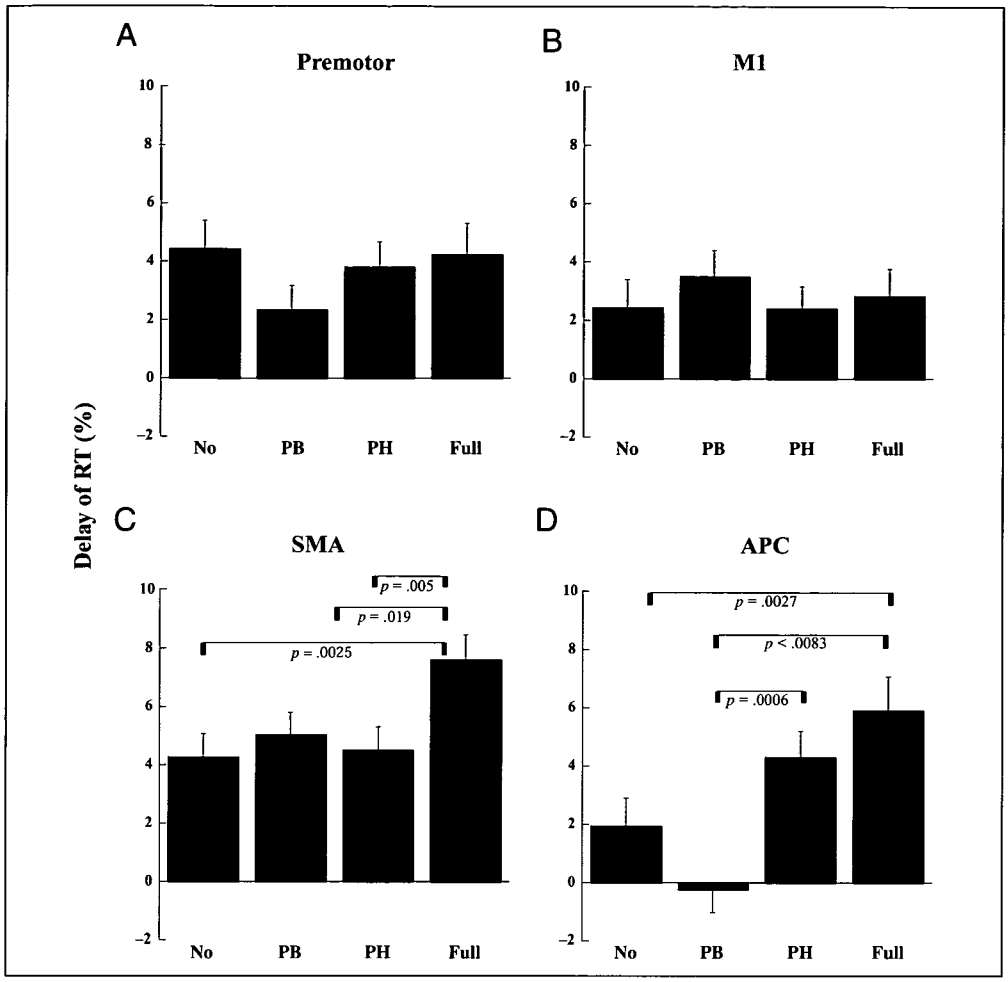

Figure 6. Effect of advance information on the rTMS aftereffect. The aftereffect was plotted separately for conditions of different precue information. Advance information did not significantly affect the aftereffect when rTMS was applied over the (A) premotor and (B) motor cortices. In contrast, it did influence the aftereffect when rTMS was delivered over the (C) SMA and (D) APC. Brackets indicate pairs of significant difference.

reached significance [$F(1,5) = 4.569, p = .0327$], reflecting an overall larger RT delay induced in left-hand responses, whereas the interaction between hand and the hemisphere stimulated failed to do so [$F(1,5) = 0.889$, $p = .35$] (Figure 7B). This latter finding suggested that regardless of which hemisphere was stimulated, the effect of rTMS was larger on left-hand responses.

For the motor cortex (Figure 7A), on the other hand, the aftereffect of rTMS was significantly larger over the left hemisphere than over the right hemisphere throughout the followed-up time points [effect of hemisphere stimulated: $F(1,5) = 24.415, p < .0001$; interaction between time and hemisphere $F(1,25) = 0.778, p = .57$]. Although, again, the rTMS effect appeared larger on left-hand responses, the effect of hand failed to reach significance [$F(1,5) = 1.497, p = .22$].

From Figure 7B, we note a hemispheric difference for rTMS effect, in which rTMS over the left hemisphere M1 induced comparable effects on left- and right-hand responses, whereas rTMS over the right hemisphere M1 exerted a larger effect on left-hand responses. Nevertheless, the interaction between the hand and the hemisphere stimulated failed to achieve significance [$F(1,5) = 0.992, p = .32$]. Thus, we compared the effect of rTMS over the motor and premotor cortices by pooling the data for both of these cortical areas. As shown in Figure 7, for M1, the stronger effect of rTMS on left-hand responses when it was given over the right hemisphere was largely diminished when rTMS was given over the left hemisphere (Figure 7B), whereas for the premotor cortex, the effect of rTMS was equally stronger on left-hand responses whether it was delivered over the left or right hemisphere (Figure 7D). Namely, there was greater trend toward contralateral predominance for rTMS over M1 than that over the premotor cortex.

Experiment 3: Comparison of the rTMS Aftereffects among Unilateral rTMS Over the Left Hemisphere Premotor and Motor Cortices and SMA

The overall magnitude of aftereffect was largest for rTMS over the SMA, then over the premotor and motor cortices [effect of site: $F(2,18) = 5.179, p = .057$; significant difference between SMA and other regions, $p < .0167$, no significant difference between premotor and motor cortices, $p = .400$]. Again, the aftereffect of rTMS displayed a biphasic time course, one peak within 10 min and another

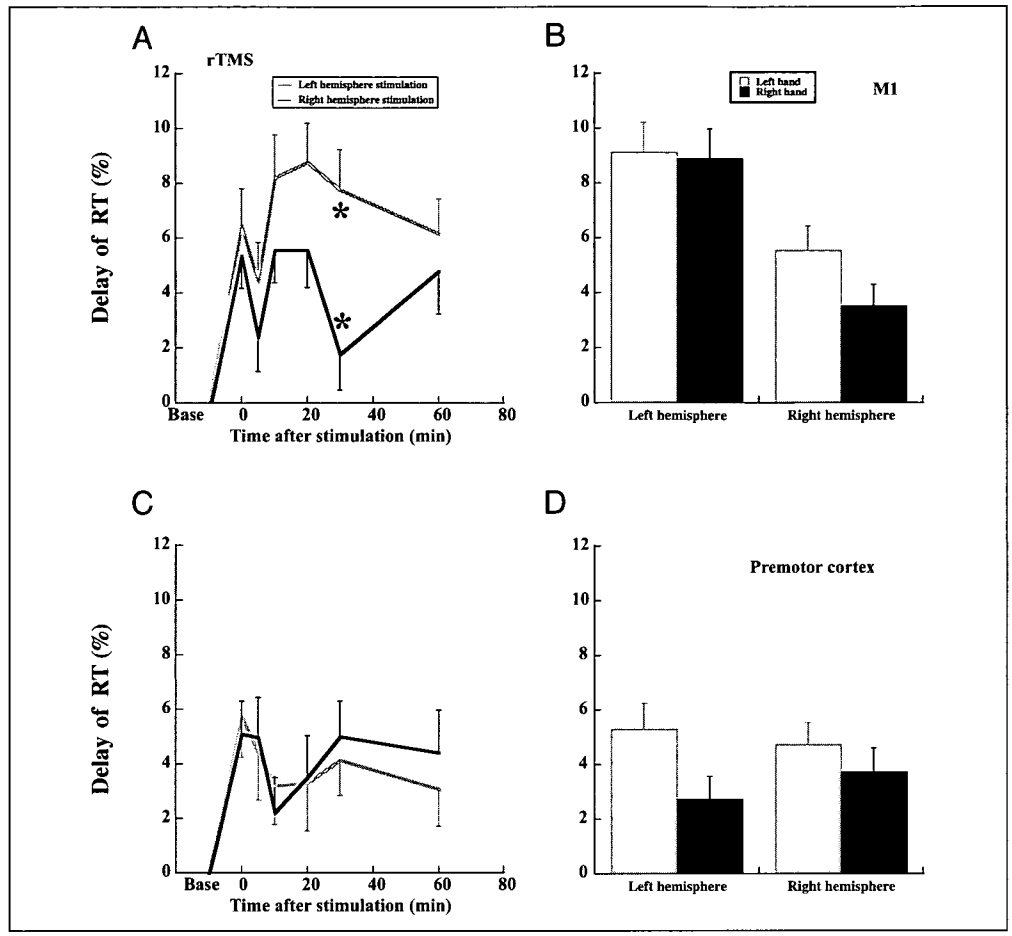

Figure 7. Laterality of rTMS aftereffect over the motor and premotor cortices. Time courses of aftereffect over the (A) motor and (C) premotor cortices. Gray and black solid lines indicate rTMS over the left and right hemispheres, respectively. Base = prestimulation baseline. *Significant difference between the bilateral motor cortices. The aftereffect on left- and right-hand responses when rTMS was applied over the (B) motor and (D) premotor cortices.

peak at 20 to 30 min whether TMS was applied over the premotor or motor cortex or over the SMA (shown by asterisks in Figure 8A). Notably, the aftereffect was not significant relative to baseline after 10 min of rTMS.

We now looked at the effect of precue information on the delay induced by rTMS (Figure 8B). Over the premotor cortex, the delay induced by TMS, expressed in percentages of the baseline RT was slightly larger in the no-information condition than in the full-information condition, although this difference barely failed to achieve significance [$F(1,9) = 3.589, p = .058$]. In contrast, over the SMA, TMS induced a slightly greater delay in the full-information condition as compared with no formation condition [$F(1,9) = 4.735, p = .030$]. On the other hand, the delay induced over the motor cortex was comparable for the two conditions [$F(1,9) = 0.004, p = .949$]. Again, MT did not deviate significantly from the baseline value at any time interval after stimulation ($p > .05$).

DISCUSSION

Effect of rTMS on the Cortical Network for Motor Preparation

The present study demonstrated that rTMS has a significant effect on motor preparation when applied bilaterally over the lateral convexity, that is, over the premotor and motor cortices and APC, as well as over the midline cortical areas including SMA. The distribution of effective regions coincides with the cortical network described as participating in motor preparation or selection (Adam et al., 2003; Deiber et al., 1991, 1996). The prolongation of RT accords with the notion that inhibitory 1-Hz rTMS produces a lasting decrease in regional excitability and impairs efficient neuronal processing within the stimulated area beyond the time of stimulation (Chen et al., 1997, 2003).

Even applied over a focal cortical region, rTMS is expected to exert a complex effect on various regions. rTMS over one cortical area can affect function not only of that local area but also the processing taking place in other regions by a spread through cortico-cortical or corticosubcortical projections (Chouinard, Van Der Werf, Leonard, & Paus, 2003; Ilmoniemi et al., 1997). Furthermore, preparation and execution of praxis movements involves a distributed network interconnecting the parietal, premotor, and motor cortices (Wheaton, Shibasaki, & Hallett, 2005; Hanna-Pladdy et al., 2001). Thus, stimulating any single cortical region would result in a "distributed" effect throughout the entire network (Murase, Duque, Mazzocchio, & Cohen, 2004; Civardi et al., 2001). Indeed, single-pulse TMS given while the

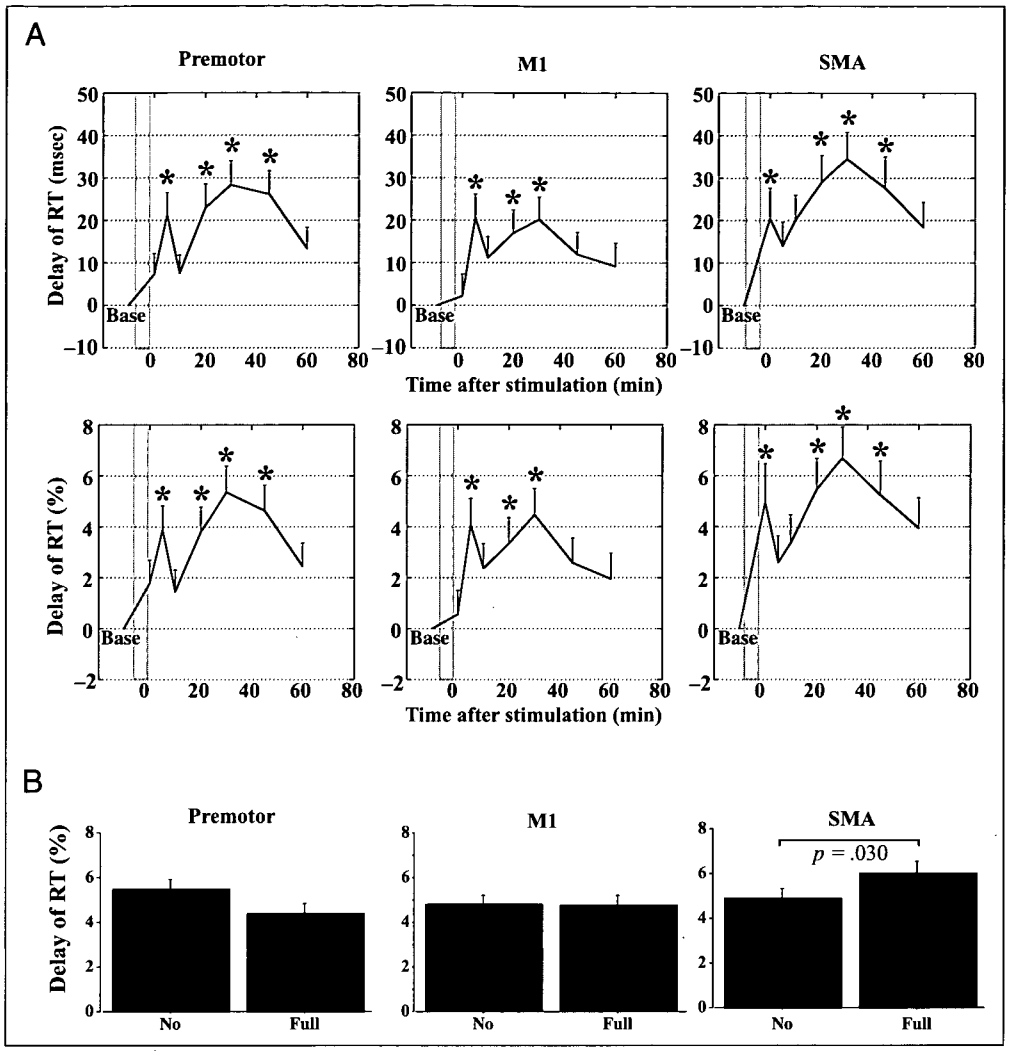

Figure 8. The rTMS aftereffect after unilateral stimulation of the left hemisphere premotor and motor cortices and SMA. (A) Time courses of rTMS aftereffect after unilateral stimulation of the left hemisphere premotor (left) and motor cortices (middle) and SMA (right). Base = prestimulation baseline. Other conventions as in Figure 2. (B) In each plot, the aftereffect in terms of RT ratio is plotted separately for conditions of two different precue information (no- and full-information conditions). Brackets denote pairs of significant difference.

subjects performed the precued-choice RT task ("on-line paradigm") resulted in similar effects on RT when applied over various areas of the frontal and parietal lobes (Terao et al., 2005).

This study for the first time compared the TMS effects on the same task using the on-line and off-line paradigms, which shed light on different aspects of cortical processing. The important finding was that the focality of effect was actually more evident with rTMS, although we would have expected the contrary, as discussed above. In addition, different effects were obtained on motor preparation, depending on which area was stimulated. For example, stimulating M1 had similar effects across different precues, whereas stimulating the SMA or APC had very different effects, depending on the precue information (Figure 6). The rTMS aftereffect presumably modulated the function of stimulated local area more strongly and in a more lasting manner than that of other regions interconnected with it. Because the time of stimulation was separated from that of task performance, the disruption of performance mainly reflected the "persisting" effect on the stimulated region, whereas the effect on other cortical areas would have largely dissipated. In the on-line paradigm, the effect of single-pulse TMS would be immediately conveyed to other areas just during the time the task is being performed, and the cortical network is active and would thus disrupt task performance wherever in the network TMS is applied. Whereas the different mechanisms of actions of single-pulse TMS and rTMS warrant further investigation, the unexpected focality of rTMS effect has an important implication for its clinical application.

Biphasic Modulation of rTMS Aftereffect

The rTMS aftereffect in the present study lasted for up to 60 to 90 min and displayed a biphasic modulation, with one peak within 10 min followed by another between 20 and 30 min after the stimulation. In contrast, documented aftereffects of rTMS on motor behavior or functional EEG coupling are invariably monophasic, lasting up to 30 min after stimulation (Huang et al.,

2005; Chen et al., 2003; Muellbacher et al., 2000). The longer duration of our effect compared with those of previous studies may be ascribed to the long stimulus train we used in this study.

To our knowledge, this is the first observation of biphasic modulation of the rTMS aftereffect. It is possible that this modulation resulted from the protocol we used in Experiment 1 for stimulating the lateral convexity, namely, one hemisphere was stimulated after another with a delay of 20 min; if we assume a similar dynamic for the two stimulations, the first peak of effect may have arisen from the first stimulated hemisphere and the later peak from the second hemisphere, which were superimposed on each other. However, this does not explain the fact that a similar biphasic modulation of aftereffect was noted for the midline cortical regions (SMA and Cz) where stimulation was continuous for 40 min. Furthermore, we also observed a biphasic modulation in Experiment 2, where the motor and premotor cortices of each hemisphere were stimulated separately, and not one after another. On the other hand, the two phases of modulation differed largely in duration, with the first peak lasting for 5 to 10 min and the second lasting for 30 to 60 min. Superimposition of two time courses similar in shape to each other but shifted only in time would not lead to such a profile.

The fact that the two phases were noted for all the effective stimulus locations (Figure 3) suggests that all the relevant cortical areas, including the primary and secondary motor areas, have a common neural organization and physiological mechanism that, when stimulated by rTMS, gives rise to a biphasic modulation and/or that, because the relevant cortical areas are interconnected, the altered activity of the circuits intrinsic at the local cortical site spreads to remote areas through functional connections. This possibility also provides the most parsimonious explanation for the findings. In the latter case, because the stimulus intensity used was relatively low, rTMS presumably affected the ongoing activity in the connections that are tonically active, for example, altered the effectiveness of synaptic connections in the circuits intrinsic at the local cortical site, whose effect was conveyed to remote areas via corticocortical projections (see also Matsunaga et al., 2005). On the other hand, rTMS can lead to neurotransmitter release and monoamine transporter activity changes, both at the stimulated site and at brain structures interconnected with it, which, in turn, induce metabolic changes and up- or down-regulation in gene expression (Ikeda, Kurosawa, Uchikawa, Kitayama, & Nukina, 2005; Hayashi et al., 2004; Ohnishi et al., 2004; Doi, Sato, Fukuzako, & Takigawa, 2001; Hausmann, Weis, Marksteiner, Hinterhuber, & Humpel, 2000). These latter effects, however, last from 3 hr up to 1 week after stimulation and are too long to correlate with the duration of effects in the present study.

Changes in the efficacy of local cortical synapse have been proposed as one of the most plausible mechanisms of the rTMS aftereffect (Takano et al., 2004; Münchau et al., 2002). We also have preliminary data showing that the excitability of the motor cortex exhibits a biphasic modulation of excitability with a similar time course after rTMS, which indicates that the actual modulation occurs at the level of synapse. Indeed, at the neural level, target-cell specific regulation of synaptic signaling has been proposed as responsible for the short-term modification of postsynaptic potentials (Gao & Goldman-Rakic, 2003). On the other hand, Touge, Gerschlager, Brown, and Rothwell (2001) investigated motor cortical excitability after 150 to 1500 rTMS pulses at 1 Hz over the motor cortex and obtained a reduction in MEP amplitude, although this reduction was not observed in MEPs evoked in actively contracting muscles. Based on this finding, they suggested that the suppression was not because of suppressed transmission in synaptic connections to pyramidal cells activated by the test TMS pulse. Rather, the excitability of cortical neurons was reduced in relaxed subjects, but this was normalized during voluntary contraction, which activates the excitability levels of the neurons. On the other hand, Takano et al. (2004) delivered 5-Hz rTMS at submotor threshold intensities over the motor cortex and observed a decrease in short-latency intracortical inhibition without affecting corticospinal excitability. This decrease was ascribed to rTMS suppressing $GABA_A$-ergic synapses mediating inhibitory gain control.

How does the biphasic modulation come about? The two phases of effect may reflect altered functions of separate populations of neurons and/or synapses producing excitatory effects at different latencies. Alternatively, the two phases may also occur as a combination of excitatory and inhibitory effects, subserved again by separate populations of neurons or synapses and taking effect at different latencies. Whatever the combination of effects, we must assume a function of neural circuits that allows these two distinct modulations to occur. Some recent studies indicate the possibility that a biphasic modulation may emerge as a result of the combined regulation of the intrinsic excitability of neurons and/or neurotransmitter release at both inhibitory and excitatory terminals (see Gao & Goldman-Rakic, 2003). For example, Seamans, Gorelova, Durstewitz, and Yang (2001) applied dopamine on pyramidal neurons in the prefrontal cortex and observed biphasic effects on evoked inhibitory postsynaptic current; an initial suppression for 2 to 20 min after application was followed by a prolonged increase (>20 min after application). They also showed that D1 and D2 receptors modulated GABA-ergic activity in opposite manners and through different mechanisms in prefrontal cortex pyramidal cells. Such a biphasic modulation would lead to biphasic changes in RT, as reported in the present study, because any up- or down-regulation of the interneuronal/

synaptic activities would offset them from their "optimal" levels for cortical processing.

Differential Effect of rTMS on RT Under Different Conditions of Advance Information

The pattern of RT delays between different conditions of advance information depended on the site of stimulation. The effect of rTMS over the APC was larger for the more informative conditions, suggesting that this region plays a crucial role in the use of advance information for the specific motor preparation to perform a motor act. Deiber et al. (1996) also demonstrated greater activation of the APC in the full and partial information conditions than in the no-information condition. In primates, preparatory activity has been recorded in the inferior parietal lobule (Godschalk & Lemon, 1989), the interparietal sulcus (Requin et al., 1990), and the superior parietal lobule (Crammond & Kalaska, 1989). Thus, the parietal region, although interconnected with primary and secondary motor areas, may play a role distinct from those areas in the use of visual information for partial or complete preparation to perform motor acts.

The effect of rTMS over the SMA was also influenced by the precue information. Set-related activity is reported in the secondary motor regions, such as the premotor cortex and SMA, and that target and body-part information is integrated in these areas when planning action (Fujii, Mushiake, & Tanji, 2002; Hoshi & Tanji, 2000). Hoshi and Tanji (2004) trained monkeys to perform a behavioral task in which two instruction cues were given successively with a delay: one cue instructed the location of the reach target and the other instructed effector (right or left arm). They found neurons in the pre-SMA and some in the SMA whose activity reflected the combination of the target and effector information during the delay period. If the same holds true in humans, this explains why rTMS over the SMA–pre-SMA region was most effective on trials with full advance information.

On the other hand, rTMS over the primary motor and premotor cortices delayed RT to a similar degree across the four precue conditions. Therefore, in contrast to the APC and SMA, these areas do not appear to be primarily involved in integrating target and effector information but may rather be implicated in a process closer to the formation of motor output as discussed in the next section.

Wheaton et al. (2005) investigated cortico-cortical coherence during the preparation of praxis movements of the hand. Electrodes over the premotor cortex showed coherence with the hand motor area and the parietal cortex but not with the SMA, those over the parietal region with the premotor cortex and the SMA but not with M1, whereas those over the SMA showed coherence to the motor and parietal regions but not to the premotor area. To explain the pattern of interregional coupling, the authors postulated a functional connectivity in at least two distinct paths: a parietal–premotor–motor path and a parietal–supplementary motor–motor path. This dual-path hypothesis accounts for the significant effect of advance information in the latter path and lack thereof in the former path as shown in the present study.

Contribution of the Premotor and Motor Cortices to Motor Preparation

How do the premotor and motor cortices contribute to motor output? To address this question, we studied the laterality of rTMS effect when the coil was placed over the premotor and motor cortices of both hemispheres. Any effect directly related to motor output per se should exhibit contralateral predominance, with rTMS over the left hemisphere predominantly influencing the right-hand responses and vice versa. In contrast, an effect closer to higher motor processing, such as motor preparation or motor programming, would present with left hemispheric predominance regardless of the response hand, given the left hemispheric dominance for programming motor skills in right-handers (Haaland & Harrington, 1996; Goodglass & Kaplan, 1983; De Renzi, Faglioni, & Sorgato, 1982; Kimura & Archibald, 1974; de Ajuriaguerra, Hécaen, & Angelergues, 1960; Liepmann, 1920). We did not obtain a pattern of hemispheric effect that clearly matches either of the hypotheses but observed a difference in the aftereffects between the hands used for the task. The aftereffect of rTMS was almost invariably larger on left-hand than on right-hand responses over the effective regions throughout all the investigated time points. This finding may be explained by the heavier load for processing nondominant left-hand than dominant right-hand movements, because the subjects recruited in this study were all right-handed.

The overall aftereffects of rTMS over the premotor cortex responses were comparable when delivered over both hemispheres, with larger effect induced on left-hand responses. The bilateral contribution of premotor cortex is consistent with its dense interhemispheric connections (Wise, Boussaoud, Johnson, & Caminiti, 1997; Dum & Strick, 1991) and the fact that this area is capable of programming the motor activity of both body sides (Sabate, Gonzalez, & Rodriguez, 2004; Green, Bialy, Sora, & Thatcher, 1997).

On the other hand, the rTMS aftereffect over M1 was much larger over the left than over the right hemisphere. Over the left hemisphere, the rTMS aftereffect was comparable on both hands, whereas over the right hemisphere, the effect was larger on the right hand. The pattern is not readily compatible with the simple contralateral predominance account. Therefore, what was disrupted by rTMS over M1 is not the motor output itself but may rather be the cortical processing for the formation of motor output subserved predominantly by the left hemisphere (Hammond, Fox, & Allison, 2005; Hanna-Pladdy et al., 2001; Heilman, Meador, & Loring,

2000; Haaland & Harrington, 1996; De Renzi et al., 1982; Kimura & Archibald, 1974; Liepmann, 1920). The left hemispheric predominance of effect also accords with the asymmetry of M1 connectivity that is known to be more extensive in the left hemisphere (Guye et al., 2003).

The trend that the effect of rTMS over M1 exhibited more contralateral predominance than that over the premotor cortex would place the role of M1 at a position closer to the formation of motor output than the premotor cortex (Figure 7B). Together, the unilateral predominance of M1 would suggest that the preparation process for motor output converges mainly into the left M1, which may take over the processing in the SMA and premotor paths at their final stage regardless of the hand used.

Clinical Implications

Finally, some theoretical considerations on the clinical applications would merit discussion. Our present findings are consistent with the notion that the effect of rTMS was more powerful on motor preparation rather than on motor output per se. Although what we obtained here was a prolongation of RT, high- instead of low-frequency rTMS might be used to facilitate the cortical processing for motor programming and, thus, speed up movements (see Introduction). A beneficial effect would be expected especially when high-frequency rTMS is applied over the SMA and the APC, which have been shown to play a role in integrating target and effector information. Such a treatment could be used for neurological diseases characterized by slowed movements, such as Parkinson's disease. Because, in many of the motor actions, motor preparation takes a longer time to be completed than the motor output itself, modifying the former would have a greater impact in speeding up motor actions than affecting the latter. Although the duration of rTMS aftereffect up to 60 to 90 min is much longer than those reported in previous studies (in the range of 10–15 min), it should be admitted that the length of aftereffect is still not long enough for a practical treatment protocol, and thus optimal stimulus parameters would have to be sought to maximize the length of aftereffect. In this context, primate studies by our group points to promising possibilities toward this goal, in which the effect of high-frequency rTMS resulted in long-lasting effects up to 1 week in some brain regions (Hayashi et al., 2004; Ohnishi et al., 2004).

Throughout the two phases of modulation, the overall effect of rTMS was more pronounced on the left hand than on the right. This implies that the rTMS treatment would have a greater effect on left-hand responses, which, in clinical settings, is not always what we expect to have. Indeed, if motor programming of the nondominant hand generally taxes the relevant cortical areas other than that of the dominant hand, such an asymmetry should be an inherent problem when modifying motor preparation (see Terao et al., 2005). For rTMS, this problem may be circumvented by stimulation of homotopic regions of bilateral hemispheres, possibly at different intensities and/or frequencies, although such a protocol is necessarily more complex than the one employed in the present study and again warrants a more detailed investigation into the stimulus parameters.

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