The present study investigated whether transcranial magnetic stimulation (TMS) to the parietal cortex improves the performance of healthy persons in a spatial working memory (WM) task. The effect of TMS on the frontal cortex was examined by measuring oxygenated hemoglobin (oxy-Hb) with near-infrared spectroscopy. Fifty-two healthy persons received either 100% resting motor threshold TMS at 5 Hz (real TMS) or sham TMS while engaged in a spatial WM task or a control visuospatial attention task. TMS was applied to either the left or the right parietal cortex during the delay period of the task. Reaction times improved in the spatial WM task, but not in the control task, with real TMS, whereas sham TMS had no effect. This improvement was only observed when TMS was applied to the right parietal cortex. Application of real TMS to the right parietal cortex also significantly increased frontal oxy-Hb levels during the WM task, but reduced oxy-Hb during the control task. These results suggest that TMS to the right parietal cortex may selectively facilitate spatial WM. Hemispheric asymmetry and the frontoparietal network theory may explain the observed effect of right parietal TMS on spatial WM.

Keywords: facilitation, frontoparietal network, hemispheric asymmetry, hemodynamic effect, visuospatial attention

Introduction

Transcranial magnetic stimulation (TMS) is increasingly being used to selectively modify neural processing. Images obtained by positron emission tomography (PET) and/or functional magnetic resonance imaging (fMRI) have shown that TMS not only affects the cortex beneath the coil, but also influences distant parts of the brain that are anatomically interconnected. Paus et al. (1997) measured cerebral blood flow by PET while they stimulated the frontal eye field with 10-Hz TMS. They detected a distant effect (increase of cerebral blood flow) of TMS on the superior parietal and medial parieto-occipital regions, which are known to have connections with the frontal eye field. Fox et al. (1997) stimulated the hand area of the left primary motor cortex (M1) by TMS while recording local and remote effects with PET. Excitatory responses were observed in the ipsilateral primary and secondary somatosensory areas, in the ipsilateral ventral and lateral premotor cortex, and in the contralateral supplementary motor area, whereas there was inhibition of activity in the contralateral M1.

Working memory (WM), the cognitive process that enables humans to maintain a limited amount of information for a brief period, has been studied extensively using TMS. Both single-pulse TMS (Mull and Seyal 2001; Oliveri et al. 2001; Mottaghy et al. 2003; Nyffeler et al. 2004; Desmond et al. 2005) and repetitive TMS (Pascual-Leone and Hallett 1994; Kessels et al. 2000; Mottaghy et al. 2000, 2002; Herwig et al. 2003) have been used to investigate WM. In almost all cases, TMS has been found to cause impairment of performance, either by decreasing accuracy or by slowing the reaction time (RT). However, there have been some reports of a facilitatory effect of parietal TMS on delayed memory tasks (Kessels et al. 2000; Oliveri et al. 2001). Kessels et al. (2000) found that the RT was significantly shorter when repetitive TMS was applied to the left parietal cortex compared with application to the corresponding right cortex, although the RT was not significantly different from that for sham TMS in both cases. Oliveri et al. (2001) demonstrated that simultaneous application of single-pulse TMS to the right and left parietal cortices resulted in a faster RT than that seen without TMS. Luber et al. (2007) recently investigated the effect of TMS on a WM task by varying the frequency and timing of stimulation, as well as its location. They found that stimulation of the parietal cortex at 5 Hz during the retention phase of a delayed match-to-sample task led to a significant decrease of RT without a corresponding decrease of accuracy. Based on these studies, TMS has the potential to enhance WM task performance, but the fundamental mechanism of its effect on the cortex beneath the coil and on the interconnected remote areas is still unknown.

Near-infrared spectroscopy (NIRS) is a recently developed technique for noninvasive functional neuroimaging. It detects changes in regional cerebral blood volume by monitoring changes of the oxygenated- and deoxygenated-hemoglobin concentrations (oxy-Hb and deoxy-Hb, respectively). The principle of NIRS is based on the modified Lambert–Beer law (Delpy et al. 1988; Maki et al. 1995, 1996). NIRS has certain advantages and disadvantages compared with other functional neuroimaging methods, such as PET and fMRI. The disadvantages of NIRS include the fact that 1) it only measures the relative change of Hb and not the absolute value; 2) it only assesses the cortex immediately beneath the probe and not deeper brain structures; and 3) it has relatively low spatial resolution. On the other hand, 3 major advantages of NIRS are as follows: 1) it is a noninvasive method and repeated measurement is possible; 2) its relatively good temporal resolution of 0.1 s enables detailed assessment of temporal changes in cerebral blood volume; and 3) the portability and compactness of the apparatus enables measurements to be obtained under natural conditions, with the subject sitting in a comfortable chair. Considering the advantages and disadvantages described above, NIRS is particularly useful for assessing dynamic changes of cortical activation in response to TMS. Using NIRS, Noguchi et al. (2003) and Oliviero et al. (1999) have studied the local effects of TMS, whereas Chiang et al.
followed by a delay period of 8 s. Subsequently, a red square (1.5 cm in number (i.e., 5 "yes" trials and 5 "no" trials).

"Yes" and "no" trials were pseudorandomized to be equal in number. The probe cue was identical to the location of any target cues based on the retention phase or during presentation of the recognition probe. Significant speeding of RT occurred in the retention phase but not the probe phase. Based on these previous findings, we hypothesized that applying TMS to the parietal cortex at 5 Hz during the retention period would optimize the performance of a spatial WM task. We also used concurrent TMS-NIRS to measure the regional cerebral blood volume and changes of Hb in the broad frontal region to assess the distant effects of TMS during the task.

Materials and Methods

Subjects

Fifty-two healthy persons (30 men and 22 women) with a mean age of 23.4 ± 2.7 years were recruited as paid volunteers. All of the participants were right handed, as determined by the modified Edinburgh Handedness Questionnaire (Oldfield 1971), and had normal or corrected-to-normal vision. Potential subjects were excluded if they had a history of neurological or psychiatric disorders, including substance abuse/dependence. All subjects were screened for depression with Zung's Self-rating Depression Scale (Zung 1965), and those who scored 40 or above were excluded from the study. This study was approved by the Ethics Committee of Showa University School of Medicine. All of the participants gave informed consent after being given a full description of the study. Participants were randomly divided into 2 groups, depending on the parietal sites for TMS. Two sites, P3 in the left parietal cortex and P4 in the right parietal cortex were chosen for stimulation in this study, based on the international 10-20 system (Klem et al. 1999). Twenty-seven subjects received TMS at P3 and 25 subjects received TMS at P4.

Tasks

Participants were trained to perform 2 delayed match-to-sample tasks (a spatial WM task and a control [Cont] task), which were presented on a personal computer (Inspriron XPS M1710; Dell, Round Rock, TX). Each trial lasted for 42 s and followed a predetermined sequence of phases (Fig. 1).

Spatial WM Task

The trial commenced with a black background and a central fixation image (white cross, 1 x 1") that turned pink as a warning signal. After a warning interval (2 s), 4 red squares (1.5 x 1.5") were presented at peripheral locations (4 of 8 locations) as a target cue (2 s), which was followed by a delay period of 8 s. Subsequently, a red square (1.5 x 1.5") was presented as a probe cue at 1 of 8 peripheral locations for 5 s. The participants were requested to report whether the location of the probe cue was identical to the location of any target cues based on spatial WM. The "yes"-"no" response was given by pressing a button with the right index finger or the left index finger, respectively. Each trial was followed by an interval interval (ITI) of 25 s, during which a white cross was presented in the center of the display. Throughout the trial, the participants were instructed to maintain fixation on the central cross. "Yes" and "no" trials were pseudorandomized to be equal in number (i.e., 5 "yes" trials and 5 "no" trials).

Figure 1. Examples of the WM task (WM: upper row) and the control task (Cont: lower row). The upper row requires a "no" response, and the lower row requires a "left" response. The trial phases and their durations are shown at the top.

Control Task

An identical target cue consisting of red squares at 4 of the 8 peripheral locations was presented after a warning interval, followed by a delay period of 8 s. Then a red square was presented as test cue at either the right or left side of the screen and the participants were requested to press the corresponding button. "Right" and "left" trials were pseudorandomized to be equal in number. This control task required a comparable amount of attention as the spatial WM task. The 2 tasks were designed to test whether brain regions involved in the spatial WM task were specific to the WM process or to the attentional demands of the task, so the only differences between the 2 tasks were the WM process of information storage, manipulation, and updating.

Participants were requested to perform the spatial WM task or the Cont task and either real TMS or sham TMS was given during each task. The participants repeated 10 trials under each of the 4 sets of conditions (i.e., WM-Real, WM-Sham, ContReal, or ContSham). The order was counterbalanced across the participants, and a 10-min break was provided between each condition. Participants received sufficient training before actual NIRS measurement so that they were able to perform the task adequately (i.e., >80% correct responses). They were instructed to respond as quickly and as accurately as possible.

Transcranial Magnetic Stimulation

Both real and sham TMS were performed. Real TMS was applied using an air-cooled figure-8 coil (70 mm in diameter) powered by a Magstim Rapid System (Magstim Co., Whitland, UK). For sham TMS, a coil was disconnected from the system, but was placed on the participant’s head in the same way as during real TMS. Meanwhile, the active coil was placed on a steel coil holder about 30 cm above the scalp to create the sound and the vibration of TMS without actually delivering a magnetic stimulus.

The TMS stimulus intensity was set at 100% of the resting motor threshold (rMT) for the right hemisphere, which was defined as the lowest intensity needed to evoke motor potentials of at least 50 μV recorded from the first dorsal interosseus muscle after at least 5/10 stimuli. Thirty pulses of TMS were applied at 5 Hz over a retention period of 6 s with an rMT of 100% according to the published safety guidelines (Wassermann, 1998). Six seconds was the best fit TMS duration and the timing when applying the TMS during the retention period manually. A total of 300 pulses (30 x 10) were given during each session, which lasted for 7 min and 40 s.

Although the participants were told that the coil would have different outputs, the sham condition was unexpected and indistinguishable to them. We asked at the end of 4 sessions to make their best guess as to whether each condition was active or sham (accuracy range from 0/4 to 4/4). Thus, the average correct response was 54.6% for P3, and 54.3% for P4 subjects, respectively. For the sham condition, the vibration generated from the real coil leant on the steel coil holder transmitted to the sham coil, might have succeeded to produce the similar acoustic cues and the skin sensation.
To analyze the raw optical data, we first defined a 32-s period from the measurement of Hb to the data collection computer from the task control computer. Each task event (e.g., the onset of the sample cue) was also transmitted to the data collection computer via an analog-digital converter. The timing of simultaneous measurements from each of the 52 channels every 100 ms and sent to the results of the virtual registration method (Tsuzuki et al. 2007). Correlation (Okamoto et al. 2004) and was displayed on the basis of channels and the measurement points on the cerebral cortex was measured at a depth of 2–3 cm from the scalp, that is, the surface of the cerebral cortex (Hock et al. 1997; Toronov et al. 2001). The probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells, with the lowest probes positioned along the Fp1-Fp2 line according to the international 10-20 system used in electroencephalography. The 52 measuring areas are labeled ch1–ch52 from the right posterior to the left anterior. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multisubject study of anatomical cranioocerebral correlation (Okamoto et al. 2004) and was displayed on the basis of the results of the virtual registration method (Tsuzuki et al. 2007).

Raw optical data for the 2 near-infrared frequencies were recorded simultaneously from each of the 52 channels every 100 ms and sent to a data collection computer via an analog-digital converter. The timing of each task event (e.g., the onset of the sample cue) was also transmitted to the data collection computer from the task control computer.

### Near-Infrared Spectroscopy

NIRS images were obtained using a 52-channel NIRS system (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). Changes of the oxy-Hb, deoxy-Hb, and total Hb concentrations were measured by using 2 different wavelengths of near-infrared light (695 and 830 nm) to detect oxy-Hb and deoxy-Hb. The distance between the pair of emission and detector probes was 3.0 cm, and it was considered that the machine measured points at a depth of 2–3 cm from the scalp, that is, the surface of the cerebral cortex (Hock et al. 1997; Toronov et al. 2001). The probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells, with the lowest probes positioned along the Fp1-Fp2 line according to the international 10-20 system used in electroencephalography. The 52 measuring areas are labeled ch1–ch52 from the right posterior to the left anterior. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multisubject study of anatomical cranioocerebral correlation (Okamoto et al. 2004) and was displayed on the basis of the results of the virtual registration method (Tsuzuki et al. 2007).

Raw optical data for the 2 near-infrared frequencies were recorded simultaneously from each of the 52 channels every 100 ms and sent to a data collection computer via an analog-digital converter. The timing of each task event (e.g., the onset of the sample cue) was also transmitted to the data collection computer from the task control computer.

### Measurement of Hb

To analyze the raw optical data, we first defined a 32-s period from the onset of the target cue as the activation period (task: 10 s) + relax (22 s) (Fig. 2). Second, we defined 5-s periods before and after the activation period as the pre- and postactivation baseline periods, respectively. Then linear fitting was applied to the data between these 2 baselines. The moving average method was used to exclude short-term motion artifacts. The oxy-Hb data from each channel were averaged across the initial 25 s of the activation period (task + relax), which was divided into 5 time segments of 5 s each (A-1: earlier part of maintenance, A-2: latter part of maintenance, B-1: first part of reaction, B-2: second part of reaction, B-3: third part of reaction). The moving average method was applied to the data between these 2 baselines. The moving average method was used to exclude short-term motion artifacts. The oxy-Hb data from each channel were averaged across the initial 25 s of the activation period (task + relax), which was divided into 5 time segments of 5 s each (A-1: earlier part of maintenance, A-2: latter part of maintenance, B-1: first part of reaction, B-2: second part of reaction, B-3: third part of reaction). And performed the same ANOVA separately for each block to assess the sequential effect of TMS. Subsequently, the data were split into 260 groups (Block: 5 levels × Ch: 52 levels) and 2-way repeated-measures ANOVA was done separately for oxy-Hb data from each Block-Ch. Significance was set at P < 0.05 for all comparisons. Statistical analysis was performed using SPSS 16.0J for Windows software (Tokyo, Japan).

### Results

No participants reported adverse events and no seizures occurred during the experiment. RTs that were longer than 3 standard deviations from the mean were excluded from analysis as outliers.

### Task Performance

To determine whether there was a trade-off between RT and accuracy, responses were correlated. It was found that there were no significant correlations across any of the conditions (all P values > 0.05) (Fig. 3). Three-way ANOVA with 2 Site (P3 vs. P4) × 2 (Task: WM vs. Cont) × 2 (TMS: Real vs. Sham) repeated measures did not show any main effect or interactions influencing performance accuracy. For the RT, the main effect of Task (F_{1,373} = 1358; P < 0.01), the interaction effect of Site × TMS (F_{1,373} = 5.101; P < 0.024, P3: P = 0.439, P4: P = 0.017), and Task × TMS (F_{1,373} = 3.948; P < 0.048, WM: P = 0.084, Cont: P = 0.245) were significant, whereas the main effect of TMS (F_{1,373} = 1400; P = 0.238), the interaction effect of Site × Task × TMS (F_{1,373} = 3.484; P = 0.063), Task × Site (F_{1,373} = 0.101; P = 0.751) were not significant. From these results, 2-way interaction effects for Site × TMS and Task × TMS seemed to indicate that TMS effect might be different depending on the stimulating site and the task. According to these findings, we conducted 2-way repeated measures of ANOVA with 2 (Task: WM vs. Cont) × 2 (TMS: Real vs. Sham) repeated measures, separately for P3 and P4. For the RT with P3 stimulation, the main effect of Task was significant (F_{1,193} = 665; P < 0.01), whereas the main effect of TMS (F_{1,193} = 0.573; P = 0.45) and the Task × TMS interaction were not significant (F_{1,193} = 0.008; P = 0.93), indicating that...
the RT for the WM task was longer than that for the Cont task irrespective of real or sham TMS. With TMS at P4, however, the main effect of Task \((F_{1,180} = 697; P < 0.01)\), the main effect of TMS \((F_{1,180} = 6.01; P < 0.015)\), and the Task × TMS interaction \((F_{1,180} = 6.89; P < 0.009)\) were all significant, indicating that real TMS selectively shortened the RT during the WM task.

**Changes of Oxy-Hb**

Four-way repeated-measures ANOVA with Task (WM vs. Cont) × TMS (Real vs. Sham) × Block (A-1-B-3) × Ch (ch1-52) was separately conducted for TMS at P3 and P4. For TMS at P3, the main effect of Ch \((F_{51,1322} = 4.7; P = 0.001)\), the Block × Ch interaction \((F_{204,5304} = 11.1; P < 0.01)\), and the Task × Block × Ch interaction \((F_{204,5304} = 6.8; P < 0.01)\) were significant (Fig. 4a and b). For TMS at P4, the main effect of Task \((F_{1,21} = 10.3; P = 0.004)\), Block \((F_{4,96} = 5.3; P = 0.005)\), and Ch \((F_{51,1224} = 4.9; P = 0.001)\) as well as the Block × Ch interaction \((F_{204,4896} = 8.1; P < 0.01)\) and the Task × Block × Ch interaction \((F_{204,4896} = 4.7; P < 0.01)\) were all significant. The other main effects and interactions were not significant.

Because the significant interactions were mainly Block and Ch effects on oxy-Hb, the effect of TMS might have been concealed. Accordingly, focusing on the effects of TMS and Task, subsequent 3-way repeated-measures ANOVA for oxy-Hb data were conducted with Site as between-subject factor, and Task and TMS as within-subject factor. Three-way repeated-measures ANOVA showed significant main effect of Task \((F_{1,13518} = 275.9; P < 0.01)\), TMS \((F_{1,13518} = 41.3; P < 0.01)\), and interaction effect of Site × Task × TMS \((F_{1,13518} = 163.1; P < 0.01)\). For the next step, we divided the data by Site factor, and performed the 2-way repeated-measures ANOVA with the factors of Task and TMS separately for P3 and P4. For TMS at P3, the main effect of Task was not significant \((F_{7019} = 0.24; P = 0.876)\), but the main effect of TMS \((F_{7019} = 34.8; P < 0.01)\) and the Task × TMS interaction \((F_{7019} = 133.4; P < 0.01)\) were significant, indicating that real TMS caused a decrease of oxy-Hb during the WM task \((F_{7019} = 160.4; P < 0.01)\), whereas it increased oxy-Hb during the Cont task \((F_{7019} = 14.2; P < 0.01)\). On the other hand, when TMS was done at P4, the main effect of Task \((F_{6499} = 475.9; P < 0.01)\), the main effect of TMS \((F_{6499} = 11.9; P < 0.01)\), and the Task × TMS interaction were significant \((F_{6499} = 49.0; P < 0.01)\). The effect of TMS at P4 was opposite to that at P3, because real TMS increased oxy-Hb during the WM task \((F_{6499} = 5.7; P = 0.017)\), whereas it decreased oxy-Hb during the Cont task \((F_{6499} = 58.8; P < 0.01)\).

The serial effects of TMS on oxy-Hb throughout blocks A-1 to B-3 are shown in Figure 5. With real TMS at P3, oxy-Hb was increased during the early retention (A-1) stage of the WM task, but it was reduced from A-2 to B-3. In contrast, real TMS had no effect on oxy-Hb during A-1, but increased it from A-2 to B-3 during the Cont task (A-1: Task × TMS, \(P = 0.121\), WM: \(P = 0.032\) [increased]; Cont: \(P = 0.920\); A-2: Task × TMS, \(P < 0.01\), WM: \(P < 0.01\) [reduced]; Cont: \(P = 0.015\) [increased]; B-1: Task × TMS, \(P < 0.01\), WM: \(P < 0.01\) [reduced]; Cont: \(P = 0.037\) [increased]; B-2: Task × TMS, \(P < 0.01\), WM: \(P < 0.01\) [reduced]; Cont: \(P = 0.164\); B-3: Task × TMS, \(P < 0.01\), WM: \(P < 0.01\) [reduced]; Cont: \(P = 0.021\) [increased]). Real TMS at P4 caused an increase of oxy-Hb during A-1 of the WM task, but its effect diminished thereafter. In contrast, real TMS had no effect on oxy-Hb during A-1, but reduced it from A-2 to B-3 during the Cont task (A-1: Task × TMS, \(P < 0.01\), WM: \(P < 0.01\) [increased]; Cont: \(P = 0.707\); A-2: Task × TMS, \(P < 0.01\), WM: \(P = 0.489\); Cont: \(P = 0.014\) [increased]; B-1: Task × TMS, \(P < 0.01\), WM: \(P = 0.374\), Cont: \(P < 0.01\) [reduced]; B-2: Task × TMS, \(P < 0.01\), WM: \(P = 0.689\), Cont: \(P < 0.01\) [reduced]; B-3: Task × TMS, \(P < 0.01\), WM: \(P = 0.124\), Cont: \(P < 0.01\) [reduced]). Because TMS was applied during the initial 6 s of the retention period, which almost corresponded to A-1 and A-2, it was clear that TMS of the parietal cortex caused changes of oxy-Hb in the frontal region during the retention period. Interestingly, the pattern of oxy-Hb changes was opposite for TMS at P3 and P4.

When additional 2-way (Task × TMS) ANOVA was conducted separately for Block-Ch data, significant Task × TMS interaction effects on oxy-Hb were detected, as shown in Figure 6. The blue and red squares in each block indicate channels with a decrease or increase of oxy-Hb due to the Task × TMS interaction effect, respectively. The effect of TMS was specific to each hemisphere throughout the task. The Task × TMS interaction effects were in the same direction throughout the blocks for TMS at P3 or P4. With TMS at P3, the interaction led to a decrease of oxy-Hb during the WM task and an increase during the Cont task, except for ch20 in A-1. With TMS at P4, the interaction led to an increase of oxy-Hb during the WM task and a decrease during the Cont task. Overall interaction effects were opposite between P3 and P4, and none of the Block-Ch effects between P3 and P4 overlapped each other.
With TMS at P3, the cortical areas corresponding to the channels were the left precentral gyrus and superior frontal gyrus during the retention period, as well as the bilateral precentral gyrus, right inferior frontal gyrus, bilateral temporal pole, supratemporal gyrus, and orbital part of frontal gyrus during the reaction period. With TMS at P4, the relevant areas were the left precentral gyrus and left marginal gyrus during the retention period, as well as the right marginal gyrus, right precentral gyrus, and superior frontal gyrus during the reaction period.

**Discussion**

In the present study, we demonstrated that application of 100% rMT-TMS at 5 Hz to the right parietal cortex during the retention period decreased the RT in the WM task. These results are consistent with previous studies supporting such an effect of TMS. In addition, there was a task-specific hemispheric difference of the influence of parietal TMS on the distant frontal areas as revealed by concurrent NIRS. On the other hand, there was no significant influence of TMS on the accuracy of task performance. The reason might be that the subjects all practiced the task beforehand until they exceeded 80% accuracy. Additionally, because of its continuous nature, RT may be a more sensitive measure of motivation than accuracy (McCaffrey 2000; Collie et al. 2003).

When TMS was applied to the left parietal cortex, it did not affect the RT during both the WM and Cont tasks. In contrast, TMS to the right parietal cortex selectively improved the RT during the WM task, but not the Cont task. These results imply that TMS of the right parietal cortex may potentially speed up the processes of information storage, manipulation, and
Updating of WM. This facilitation appears to result from a direct effect of real TMS on the underlying parietal cortical tissue, but nonspecific effects of TMS should also be considered. For example, Pasqual-Leone and Hallett (1994) reported that a single TMS pulse to the motor cortex immediately before the cue shortened the RT in a simple task. However, the same facilitation was also produced by sham stimulation. Similarly, Terao et al. (1997) suggested that effect of TMS in shortening the RT could be explained by nonspecific intersensory facilitation, such as the audible clicking of the TMS coil. However, the results of the present study could not be explained by intersensory facilitation, because the similar acoustic cues and skin sensation were present at under both real and sham conditions.

NIRS clearly demonstrated that both right and left parietal TMS during the retention period of the task caused changes of oxy-Hb in the frontal region, although the pattern of change was opposite between TMS at P3 and P4 in every block, and none of the activated or suppressed channels overlapped each other between P3 and P4. This suggests that the effect of TMS was asymmetric and lateralized, and that TMS of the right parietal cortex was optimal for enhancing spatial WM performance. The Task × TMS interaction map for oxy-Hb in each block also revealed sequential and regional characteristics. When TMS was applied to P3, it mainly altered oxy-Hb in the bilateral temporal regions during the reaction period. In contrast, TMS of P4 led to an increase of oxy-Hb during the retention period of the WM task in the left precentral and marginal gyr, after which activation subsequently shifted to the contralateral homonymous areas together with activation of the superior frontal gyrus during the reaction period (B-1 and B-2). The present findings strongly suggest that applying TMS to either the right or left parietal lobe has differential and asymmetrical effects on the fronto-temporal cortical areas, consequently modulating performance of the WM task.

Why was performance facilitated by right parietal TMS, but not by left parietal TMS? Previous findings about the frontoparietal network and right hemispheric specialization may account for the present results. The frontoparietal network mediates attentional allocation to visual locations in order to facilitate visual processing (Kim et al. 2005; Fecteau et al. 2006), and plays a crucial role in the spatial WM and Cont tasks that were employed in the present study. In the intact brain, the parietal and frontal cortices are functionally connected by excitatory and/or inhibitory neurons, and applying TMS to the parietal cortex would shift the balance toward relative inhibition or excitation of the frontal cortex. Moreover, the frontoparietal network is important for interhemispheric interaction, and it is well known that right parietal-frontal connections are dominant over left parietal-frontal connections in human for various aspects of visuospatial function (Heilman and Van Den Abell 1980; Mesulam 1981; Weintraub and Mesulam 1987; Ashbridge et al. 1997; Walsh et al. 1999; Muri et al. 2000; Rounis et al. 2007).

The mechanism we propose to account for facilitation of spatial WM by TMS is illustrated in Figure 7. During the control task, reciprocal excitatory connections are activated between the parietal and frontal cortex. When TMS is applied to P3, there is partial inhibition of the frontal cortex, but the dominant right parietal cortex maintains frontal excitation and frontal oxy-Hb shows an increase. When TMS is applied to

![Figure 5. Effect on oxy-Hb of TMS at each site and time. The gray band corresponds to TMS for most of the A-1 and A-2 periods. The activation/suppression patterns during each task were opposite between TMS at P3 and P4.](http://cercor.oxfordjournals.org/)

Figure 5.
P4, however, the disruption of the dominant parietal–frontal connection leads to inhibition of activity in the frontal cortex, so there is a decrease of frontal oxy-Hb. In the present study, TMS did not influence the performance of the control task with respect to both RT and accuracy. This suggests that the control task was simple enough for the subjects to preclude TMS having an influence on their performance. The important finding was that TMS actually has a hemodynamic effect on remote, but interconnected, frontal regions, even though there was no change of behavioral performance. With the WM task, there may be an additional inhibitory connection between the visuospatial attention neurons and frontal cortex involved in further retention and decision processes. When TMS was applied to P3, it caused partial disinhibition of the frontal cortex, although overall inhibition was maintained by the dominant right inhibitory connections and oxy-Hb showed a decrease. When TMS was applied to P4, however, suppression of the dominant inhibitory connections would lead to frontal disinhibition and an increase of oxy-Hb. This putative mechanism explains the effects of TMS on both task performance and the remote changes of oxy-Hb.

Although our combined TMS and NIRS study found a robust effect of parietal TMS on frontal oxy-Hb, we did not examine the changes of oxy-Hb in the parietal cortex under the TMS coil itself. In the future, it would be interesting to place optical probes over the parietal TMS coil as well. In addition, it could be worthwhile to apply TMS to various frontal and/or temporal areas that were not stimulated in the present study.

In conclusion, the present study demonstrated that right parietal 100% rMT-TMS at 5 Hz improved the RT during a WM task, with the mechanism of this response being thought to involve hemispheric asymmetry and the frontoparietal network. Investigation of the Task × TMS interaction revealed that these 2 tasks were complementary and that specific cortical areas had to be stimulated for facilitation. We also showed that NIRS was capable of monitoring the hemodynamic effect of TMS on remote (but interconnected) brain regions, providing a suggestion about the mechanism through which TMS influences the WM task. Application of TMS to facilitate the performance of elderly and amnesic patients may eventually be possible.

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Figure 7. Possible pattern for the overall representation of visuospatial attention and WM, with the task performance and the corresponding changes of oxy-Hb. 1) In healthy individuals, reciprocal excitatory connections between the frontal and parietal areas are involved in visuospatial attention. On the other hand, reciprocal inhibitory connections exist between visuospatial attention neurons and the frontal area for retention and decision as part of WM. The right frontoparietal excitatory/inhibitory connection is usually dominant over that on the left. TMS of the parietal cortex would interfere with the frontoparietal excitatory/inhibitory connection. 2) During the control task, left parietal TMS does not disrupt the excitatory connection with the frontal area because the right excitatory connection is a dominant and compensates for the left connections, so oxy-Hb is increased. Right parietal TMS induces a reciprocal inhibitory connection with the frontal area, because the disruption of the dominant connections excels the compensation for the right connections, so oxy-Hb is decreased. In this case, control task performance did not differ between P3 and P4 TMS. 3) During the WM task, left parietal TMS does not disrupt inhibitory connections to the frontal area because right inhibitory connections are stronger and compensates for the left connections, so the RT is not improved and oxy-Hb is decreased. On the other hand, right parietal TMS induces a reciprocal excitatory connection with the frontal area because the disruption of the dominant connections excels the compensation for the right by left connections. This activates the retention and decision parts of WM, thus improving the RT and increasing oxy-Hb.

Notes
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Address correspondence to Masaru Mimura, MD, PhD, Department of Neuropsychiatry, Showa University School of Medicine, 6-11-11 Kita-Karasuyama, Setagaya-ku, Tokyo 157-8577, Japan. Email: mimura@med.showa-u.ac.jp.

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