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Differential effect of double-pulse TMS applied to dorsal premotor cortex and precuneus during internal operation of visuospatial information

Ritz Oshio [a,b,c,d], Satoshi Tanaka [b,d,e], Norihiro Sadato [b,f], Masahiro Sokabe [a,g,h], Takashi Hanakawa [i,j], Manabu Honda [d,i,*]

[a] Department of Physiology, Graduate School of Medicine, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[b] Laboratory of Cerebral Integration, National Institutes for Physiological Sciences, 38 Nishigonaka, Myodaiji-cho, Okazaki 444-8585, Japan
[c] Graduate School of Informatics, Kyoto University, Kyoto, Gokasho, Uji, Kyoto 611-0011, Japan
[d] Japan Science and Technology Corporation (JST), SORST, 4-1-8 Honmachi, Kawaguchi, Saitama 331-0012, Japan
[e] Research Center of Advanced Technology and Science, The University of Tokyo, 4-6-1, Komaba, Meguro-ku, Tokyo 153-8904, Japan
[f] Japan Science and Technology Agency (JST), RISTEX, 4-1-8 Honmachi, Kawaguchi, Saitama 331-0012, Japan
[g] Japan Science and Technology Agency (JST), ICORP/SORST Cell Mechanosensing, 4-1-8 Honmachi, Kawaguchi, Saitama 331-0012, Japan
[h] Department of Molecular Physiology, National Institutes for Physiological Sciences, 38 Nishigonaka, Myodaiji-cho, Okazaki 444-8585, Japan
[i] Department of Cortical Function Disorders, National Institute of Neuroscience, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan
[j] Japan Science and Technology Agency (JST), PRESTO, 4-1-8 Honmachi, Kawaguchi, Saitama 331-0012, Japan

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ABSTRACT

Human neuro-imaging studies have often reported co-activation of the dorsal premotor cortex (PMd) and the posterior parietal cortex (PPC) during internal operation of visuospatial information, referred to here as "visuospatial mental operation". However, the functions assigned to the PMd and PPC during these tasks are still unclear. Here, we examined the significance of these two areas for a visuospatial mental operation using the transcranial magnetic stimulation (TMS) technique. Subjects performed a task in which a visuospatial mental operation was required. A localization study conducted prior to the TMS experiment using functional magnetic resonance imaging (fMRI) revealed that the PMd and the medial part of the PPC, precuneus (PCu), were specifically activated during the visuospatial mental operation. Then, we impeded the activities of the PMd and the PCu in the right hemisphere during the same task using double-pulse TMS to determine whether these activities were necessary for the task. The TMS was applied at different times in relation to the visuospatial mental operation cue. Consequently, only the TMS applied at 300 ms after the cue affected the task performance. Furthermore, we found that the TMS at this time to each area differentially affected the performance: TMS to the PMd hindered the performance of the task whereas TMS to the PCu facilitated it without a speed/accuracy trade-off. These effects were not found in the control condition that lacked a visuospatial mental operation. These findings suggest that the PMd and the PCu are involved in differential aspects of visuospatial mental operations.

Introduction

Internal visuospatial behaviors, such as mental rotation, action imagery and mental rehearsal, referred to here as "visuospatial mental operation (VSMO)", have an important role in everyday cognition. Indeed, tasks involving visuospatial mental operations form an essential component of many intelligence tests e.g., Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). Many human neuro-imaging studies have reported that such mental operation processes activate the fronto-parietal networks (Hanakawa et al., 2003a,b; Hanakawa et al., 2002; Hanakawa et al., 2003c; Kosslyn et al., 1998; Meister et al., 2004); however, the functional role of each area remains unclear. Interestingly, the activated brain regions, especially the premotor cortex (PM) and posterior parietal cortex (PPC), considerably overlap the regions activated during execution of visuomotor tasks (Hanakawa et al., 2003c; Sirigu et al., 1996; Wise et al., 1997). Based on studies of the motor control domain, the PM has been implicated in generating or simulating movement sequences to plan movements before the actual movement in a "feed-forward" manner (Cisek and Kalaska, 2004; Ohbayashi et al., 2003; Seidler et al., 2004). On the other hand, studies of target-directed behavior such as reaching or saccades have shown the involvement of the PPC in online movement monitoring to evaluate and correct the movement in a "feedback" manner (Fattori et al., 2001; Galletti et al., 2003; Grea et al., 2002; Perenin and Vighetto, 1988). These findings suggest that the PM

* Corresponding author. Department of Cortical Function Disorders, National Institute of Neuroscience, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan. Fax: +81 42 346 1748.
E-mail address: honda@ncnp.go.jp (M. Honda).

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and the PPC play different roles in visuomotor control. However, the functional difference between the PM and the PPC during the visuospatial mental operation process is still unclear. Furthermore, which subdivision in the PM and the PPC is involved in the process is also unclear. Therefore, we hypothesized that, in analogy with the motor control domain, the PM and the PPC play differential roles in non-motor visuospatial mental operations. To evaluate this hypothesis, we used a double-pulse transcranial magnetic stimulation (TMS) technique that can induce "virtual lesion" effects (Chen et al., 1997; Hallett, 2000; Muri et al., 2002; Pascual-Leone et al., 2000; Prime et al., 2008; Sack and Linden, 2003).

The aim of the present study was to clarify the different involvement of the PM and the PPC and their functional relevance during a visuospatial mental operation. We used a combined approach of functional magnetic resonance imaging (fMRI) and subsequent TMS in the same set of subjects with the aid of a frameless stereotactic system. This combined approach enabled us to test the functional relevance of the fMRI activity in the visuospatial operation and to explore its temporal characteristics. The fMRI experiment showed that the dorsal PM (PMd) and the medial part of the superior parietal cortex, precuneus (PCu), were activated specifically in response to the visuospatial mental operation. Then, we causally examined the temporal dynamics of the involvement of the PMd and the PCu in the visuospatial mental operation task by delivering double-pulse TMS with a 100 ms interval between stimuli. We applied the TMS at one of four times (−1500, −500, +300 and +500 ms) related to the visuospatial mental operation cue to impede the activities of the PMd and the PCu during the task.

Materials and methods

The rules of Amidakuji

For the fMRI and TMS studies, we designed visuospatial mental operation tasks based on the popular Japanese lottery game *Amidakuji*, which is commonly used to make random pairings (also known as "Ghost Leg", Fig. 1A). In *Amidakuji*, we use a ladder-like spatial pattern composed of vertical lines and horizontal lines which bridge the vertical lines. The rules to play *Amidakuji* are: (1) choose one vertical line, (2) start tracing the line downwards from its top, (3) when a horizontal line is encountered, follow it to an adjacent vertical line, (4) then trace the adjacent vertical line downward (never upward), (5) continue tracing lines in the above manner until the player reaches the bottom end of a vertical line, i.e., the goal. The player does not know the goal in advance, but needs to find it by performing rule-based local tracing. Thus, online evaluation of the operation relative to the target, which is necessary for target-directed visuomotor behavior, is less critical in this *Amidakuji* task.

fMRI study

Subjects

Nineteen subjects (15 males and 4 females; mean age 26, range 20–38) were included in the fMRI study. All subjects were right-handed as assessed using the Oldfield handedness questionnaire (Oldfield, 1971). None of the subjects had a history of psychiatric or neurological illness. All subjects gave written, informed consent before the experiments. The experiments were approved by the local ethics committee of the National Institute for Physiological Sciences.

Task

Subjects performed a visuospatial mental operation task (VSMO+, Fig. 1B, upper panel) and a control task in which a mental operation was not required (VSMO−, Fig. 1B, lower panel). In both VSMO+ and VSMO−, trials began with the presentation of a white fixation-cross for 1 s, followed by presentation of the *Amidakuji* pattern for 1 s as S1 (memory cue). Here, subjects were required to memorize the pattern of S1. Immediately after S1 presentation, a grid-like pattern was presented for 1 s as a mask image to avoid the afterimage of S1. Then, the horizontal lines of the mask image disappeared and subjects were asked to fixate on an image of the remaining three vertical lines for 14 s (post-S1 delay). In VSMO+, a marker indicating the starting location was then presented above one of the three vertical lines for 1 s as S2 (operation cue). In response to S2, subjects were required to perform a mental operation of *Amidakuji* according to the memorized pattern and to remember the resulting goal location. After six markers at both ends of the three lines were presented for 1 s, to avoid an afterimage of S2, subjects fixated on an image of the three vertical lines for 14 s (post-S2 delay). A marker below one of the vertical lines was then presented for 2 s as S3 (response cue). Subjects were asked to judge whether the location of S3 matched the location of the remembered goal obtained by the mental operation and to answer as quickly as possible by pressing one of two buttons with the right index or middle finger in matched or unmatched cases, respectively. In VSMO−, after the post-S1 delay, a marker was presented below one of the vertical lines as S2, and subjects were required to simply memorize the location of S2 without performing the mental operation of *Amidakuji*. After the post-S2 delay, a marker was presented below one of the vertical lines as S3, and subjects were asked to judge whether the location of S3 matched that of S2, and to answer in the

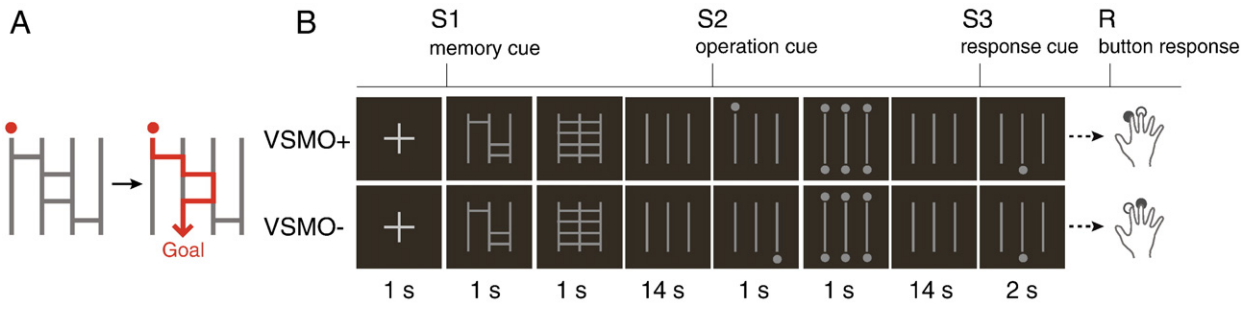

Fig. 1. *Amidakuji* rules and mental operation task in the fMRI experiment. A. *Amidakuji* and the method of operating it (red line). B. Mental operation task (VSMO+) is shown in the upper panel and control task (VSMO−) in the lower panel. In both tasks, a trial begins with the fixation-cross image. After the fixation-cross, an *Amidakuji* pattern was presented as S1 (memory cue). After S1, a grid-like image that masks the pattern was presented to avoid an afterimage effect. The horizontal lines then disappeared and subjects fixated on the vertical lines. In the VSMO+ trial, a marker indicating the starting location was presented as S2 (operation cue). In response to S2, subjects started operating *Amidakuji* in their minds and were asked to remember the goal location. After another mask image, to avoid an afterimage of S2, subjects fixated on an image of the vertical lines (post-S2 delay). Then, a marker below one of the vertical lines was presented as S3 (response cue). In response to S3, subjects judged whether the location of S3 matched the location of the remembered goal and answered by pressing one of two buttons with the right index or middle finger in matched or unmatched cases, respectively. In the control task (VSMO−), after the post-S1 delay, a marker was presented below one of the vertical lines as S2, and subjects were required to simply memorize the location of S2 without performing the mental operation of *Amidakuji* and to answer in the same way as in the VSMO+ task.

same fashion as in the VSMO+ task. After each trial, subjects were asked to fixate on a gray fixation-cross for 13 s, which then changed color to white at the start of the next trial.

The between-stimulus and between-trial intervals of 13–14 s allowed the fMRI signal generated in response to each stimulus (S1, S2 and S3) to return to baseline (Dale and Buckner, 1997). Subjects performed a total of 20 trials for each task. The trials were divided into four sessions in a randomly mixed and counter-balanced order, i.e., subjects performed 5 trials for each task in a session (total 10 trials per session) in a randomized fashion. Subjects did not know whether they were performing a VSMO+ or VSMO− trial until S2. Pairs of S2 and S3 stimuli (i.e., pair of start and goal locations) were balanced across sessions. Before the experiment with scanning, subjects performed one training session with the same stimuli as during the experimental session without actual scanning, to become familiar with the tasks and the scanner environment.

An *Amidakuji* pattern, which subtended a visual angle of 2°, was composed of three vertical lines and three horizontal lines, which bridge the vertical lines. The vertical lines were always the same, whereas the locations of the horizontal lines were varied across trials. In this study, 24 kinds of *Amidakuji* patterns were used.

For behavioral data, reaction time (RT) and accuracy were measured. RT was defined as the time between the onset of S3 and the subject's button response. Accuracy of the task performance was defined as the proportion of correct trials to the total number of trials for each task.

Data acquisition and analysis

The fMRI experiment was conducted using a 3.0 Tesla MRI scanner (MAGNETOM Allegra, Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted echo planar imaging sequence (TR/TE/flip angle/field of view/voxel size/slice number = 2000 ms/30 ms/75°/192 mm/3.0×3.0×4.0 mm/34 axial slices). A high-resolution structural image was acquired using magnetization-prepared rapid acquisition in a gradient echo (MPRAGE) sequence. Presentation software (Neurobehavioral Systems, Albany, CA) was used for the presentation of the visual stimulus and to record the responses of subjects. Stimuli were presented on a screen using a liquid crystal display projector, and subjects viewed the screen through a mirror. A total of 246 functional images were collected during each session, and the first six images were discarded from data analysis to allow for the stabilization of the magnetization. SPM2 software (Wellcome Department of Cognitive Neurology, London, UK) was used for image processing and analysis. To reduce head-motion artifacts, the functional images were realigned to the first functional image (Friston et al., 1995a). The images were smoothed spatially using an isotropic Gaussian kernel of 8 mm full-width half-maximum to increase the signal-to-noise ratio.

To clarify the brain areas involved in the mental operation process, we compared activities related to S2 in VSMO+ and those in VSMO− ("S2-VSMO+ > S2-VSMO−"). We also compared activities related to the memory cue and those related to the operation cue ("S2-VSMO+ > S1-VSMO+"). This comparison was performed to identify activity specific for the operation rather than memory, since the mental operation process is a memory-based process and the comparison "S2-VSMO+ > S2-VSMO−" may include both activities related to memory and operation. Data analysis was performed using the general linear model implemented in SPM2 (Friston et al., 1995b). For task-related brain activities, we focused on the transient activities related to the onset of each stimulus (S1, S2 and S3) and the sustained activities related to the duration of the post-S1 and post-S2 delays. Then five events (S1, post-S1 delay, S2, post-S2 delay and S3) of each VSMO+ and VSMO− were modeled using boxcar functions convolved with a canonical hemodynamic response function. Thus, regression coefficients for ten regressors (that is, five for each task) were estimated. "S2-VSMO+ > S2-VSMO−" was investigated by calculating the *t*-deviate at each voxel using the contrast '1' for S2-VSMO+, '−1' for S2-VSMO− and '0' for others, whereas "S2-VSMO+ > S1-VSMO+" was investigated using the contrast '−1' for S1-VSMO+, '1' for S2-VSMO+ and '0' for others. Group analysis of all but one subject was performed using anatomical normalization (Friston et al., 1995a) and a random effect model (Friston et al., 1999). One subject was excluded owing to the failure of the normalization step in the SPM analyses; however, individual analysis of the subject without normalization showed the same activities found in the group analysis. The voxel-wise threshold was set at $p<0.05$ corrected for multiple comparisons, with an extent threshold of 50 contiguous voxels.

To confirm the temporal characteristics of the PMd and the PCu during VSMO+, region of interest (ROI) analysis was performed using an original index named the Temporal Asymmetry Index (TAI). TAI is defined by:

$$\mathrm{TAI} = (\mathrm{PS2} - \mathrm{PS1}) / (\mathrm{PS2} + \mathrm{PS1})$$

Where: PS1 and PS2 represent the peak height of percent signal increase following S1 from baseline and that following S2 from the onset of S2, respectively. A TAI greater than 0 represents increased activity from S1 (memory cue) to S2 (operation cue). TAI were calculated from data in the VSMO+ task. ROIs of the PMd and the PCu in both hemispheres were defined by using "S2-VSMO+ > S1-VSMO+". We also examined the TAI of the lateral part of the superior parietal lobule, LPs (Note: while the PCu is also located in the superior parietal lobule, LPs is used here as the abbreviation of the "lateral" part of superior parietal lobule). ROIs of the LPs in both hemispheres were defined using "S2-VSMO+ > S2-VSMO−", since LPs activities were not detected in "S2-VSMO+ > S1-VSMO+".

TMS study

Subjects

Ten subjects (8 males and 2 females; mean age 25.6, range 20–38) who participated in the fMRI study also agreed to participate in the TMS experiment. The experiments were approved by the local ethics committee of the National Institute for Physiological Sciences.

Task

The tasks used for the TMS experiment were essentially the same as those used for the fMRI experiment (Fig. 2). Subjects performed the VSMO+ and VSMO− tasks (Fig. 2, upper and lower panels, respectively). Both the VSMO+ and VSMO− trials began with the visual presentation of a white fixation-cross for 500 ms. Following the fixation-cross, the *Amidakuji* pattern was presented for 500 ms as S1 (memory cue). Immediately after S1 presentation, a grid-like pattern was presented for 500 ms as a mask image to avoid the afterimage of S1. Then, horizontal lines of the mask image disappeared and subjects were asked to fixate on an image of the remaining four vertical lines for 2000 ms. In VSMO+, a marker indicating the starting location was then presented above one of the four vertical lines for 500 ms as S2 (operation cue). In response to S2, subjects were required to perform a mental operation of *Amidakuji*, according to the memorized pattern, and to report the resulting goal location as quickly as possible. In contrast with the fMRI experiment, subjects reported the goal location by pressing one of four buttons with one of the four fingers (second to fifth fingers) on their right hand. Each button corresponded to a goal location. After each trial, subjects were asked to fixate on a gray fixation-cross for 5 s until the start of the next trial. In VSMO−, subjects were presented with a marker below one of the vertical lines as S2 and were required to press one button corresponding to the location in the same fashion as in VSMO+. Before the experimental session, subjects performed 32 trials (half of a session) with the same stimuli as during the experimental session without TMS to become familiar with the tasks.

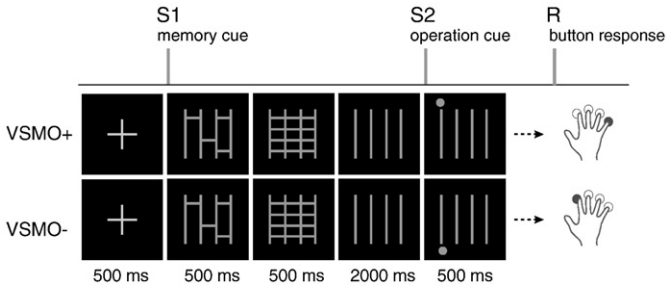

Fig. 2. The mental operation task in the TMS experiment. The mental operation task (VSMO+) is shown in the upper panel and the control task (VSMO−) in the lower panel. In both tasks, the trial begins with the fixation-cross image. After the fixation-cross, an *Amidakuji* pattern was presented as S1 (memory cue). A grid-like mask image was then presented to avoid an afterimage effect. After the masking, the horizontal lines disappeared and subjects fixated on four vertical lines. In the VSMO+ trial, a marker indicating the starting location was presented as S2 (operation cue). In response to S2, subjects started operating *Amidakuji* in their minds and pressed one of four buttons corresponding to the goal location as soon as they reached the goal (in this case, the right-most button). In the VSMO− trial, a marker indicating the goal location was presented at S2 and the subject pressed the button corresponding to the location (in this case, the left-most button). The double-pulse real or sham TMS was applied once per trial at either 1500 or 500 ms before, or 300 or 500 ms after the onset of S2.

We used smaller time intervals in the TMS study than to those used in the fMRI study due to the increased number of sampling trials required. Smaller time intervals and smaller inter-trial intervals allowed the subjects to retain their attention during these increased number of tests. In addition, the 13–14 s inter-trial interval used in the fMRI study was specifically selected to detect the event-related activities in response to each visual stimulus (i.e., S1 and S2) and to allow the MRI signal to return to baseline. There was no such requirement in the TMS study, which allowed us to shorten this time interval.

Amidakuji patterns in the TMS experiment, which subtended a visual angle of 2°, were composed of four vertical lines and four horizontal lines. The vertical lines were always the same, whereas the location of the horizontal lines varied across trials. Sixteen different *Amidakuji* patterns were used and were chosen in a randomized order.

In the TMS experiment, subjects were asked to answer the resulting goal location as soon as they finished the mental operation. This allows us to directly examine the effect of TMS on the reaction time (RT) required to achieve the mental operation. Moreover, we increased the complexity of the spatial *Amidakuji* pattern by increasing the number of vertical and horizontal lines within the pattern to increase our ability to detect the effects of TMS on reaction time and accuracy.

TMS

We tested the effects of double-pulse TMS with a 100 ms interstimulus interval (ISI) to the PMd and the PCu in the right hemisphere. The locations were identified based on the results of the preceding fMRI experiment for each subject. The target location of the PMd was defined as the point with the maximal statistical significance for mental operation versus memory ("S2-VSMO+ > S1-VSMO+") within the detected cluster situated at the conjunction of the superior frontal and superior precentral sulci. The location of the PCu was defined as the local maximal point with the detected cluster at the medial part ($x \leq 10$ mm by MNI, Montreal Neurological Institute, as reported elsewhere (Cavanna and Trimble, 2006)) of the posterior parietal cortex, as detected by the same comparison. We also applied TMS to LPs that also showed mental operation-related activities, though, unlike the PMd and the PCu, the temporal character of the activity of the LPs was not specific to S2-VSMO+. The location of the LPs was defined as the local maximal point within the cluster at the superior and lateral part of the posterior parietal cortex ($x > 10$ mm by MNI coordinate) in "S2-VSMO+ > S2-VSMO−".

To place the TMS coil on the target areas, we used a frameless stereotaxy system (Brainsight, Rogue Research, Montreal, Canada) that co-registered the subject's head position and their functional and structural MRI. Once the subject's head and MRI were co-registered, infra-red tracking was used to monitor the position of the TMS coil with respect to the subject's head position. The coil was placed and fixed on the scalp just above the target location using a mechanical holder (Point Setter, Mitaka Koki Corporation, Tokyo, Japan). The target location was marked on a tightly fitting Lycra swimming cap placed on the subject's head. The position of the coil was continuously monitored during the experiments. The coil for the sham stimulation was placed away from the scalp at the opposite side of the real stimulation coil location.

TMS was applied using a Magstim rapid stimulator (Magstim Company, Whitland, UK) with a figure-eight coil, with each wing measuring 70 mm in diameter. The intensity of stimulation was set at 70% of the maximum output of the stimulator. An ISI of 100 ms was selected to induce the inhibitory TMS effect based on previous findings that double-pulse TMS with ISIs of 60–200 ms inhibit motor-evoked potentials (Chen et al., 1997). Double-pulse sham stimulation was also applied with the same ISI at the same output intensity to control for the click noise of the TMS.

In each trial, real or sham TMS was applied at different times in relation to S2: +300 and +500 ms relative to the onset of S2. Since a preliminary behavioral experiment without TMS showed the reaction time from the S2 onset of VSMO− was 500 ms and more, we chose the two stimulation times during the visuospatial mental process from the period between the onset of S2 and 500 ms after the onset. Furthermore, we applied TMS during a period before the S2, i.e., −500 and −1500 ms relative to S2, since the fMRI results showed weak activities in the PMd and the PCu before S2.

The TMS experiments were performed on three separate days, at one stimulation site (PMd, PCu or LPs) on each day, with intervals of at least three days between experiments. In each experiment, a subject performed 16 conditions consisting of a combination of (1) task type (with or without mental operation, VSMO+/VSMO−), (2) stimulation type (real or sham stimulation), and (3) stimulation timing (−1500, −500, +300 and +500 ms relative to the onset of S2). Each condition was tested 16 times. Therefore, each subject completed a total of 256 trials in an experiment. The trials were randomly mixed and divided across four sessions in a counter-balanced manner. The order in which the locations were stimulated was pseudo-randomized and counter-balanced across subjects.

Behavioral data analysis

Reaction time was defined as the time between the onset of S2 and a subject's button response. Accuracy was defined as the proportion of correct trials to total trials of each condition. Accuracy and mean RT in the TMS condition minus those in the sham conditions were calculated for each subject (ΔAccuracy and ΔRT). The data of ΔAccuracy and ΔRT were then analyzed to examine for interactions between stimulation areas (PMd/PCu/LPs) and tasks (VSMO+/VSMO−) by two-way repeated-measures analysis of variance (ANOVA) with respect to each stimulation timing (−1500, −500, +300 and +500 ms relative to S2). Then, to examine for differences of the TMS effect among the three areas, one-way ANOVA with respect to each task (VSMO+ or VSMO−) was performed.

Results

fMRI experiment

The mean (±SE) accuracies for the VSMO− and VSMO+ tasks were 95.8 ± 2.6%, 93.9 ± 1.9%, while the mean (±SE) reaction times (RTs) were 807 ± 45 ms and 872 ± 58 ms, respectively. We first compared the activities in response to the S2-VSMO+ and S2-VSMO−

to comprehensively measure the mental operation-related activity (Fig. 3A). We found that the PMd and the LPs were activated to a greater extent during S2-VSMO+ than during S2-VSMO−. These findings are consistent with previous studies on mental operations (Hanakawa et al., 2003b; Hanakawa et al., 2002; Hanakawa et al., 2003c; Tanaka et al., 2005). Meanwhile, because mental operation is achieved by reference to a memorized pattern, the areas found in the comparison (S2-VSMO+ > S2-VSMO−) might include both memory-related and mental operation-related areas. Therefore, we next compared activities following the memory cue and those following the operation cue (S2-VSMO+ > S1-VSMO+) to identify areas activated more specifically by the mental operation than by memory (Fig. 3B). Consequently, we identified the mental operation-specific activities at the conjunction of the superior frontal and superior precentral sulci in the PMd and the medial part of the LPs, the PCu. Furthermore, a ROI analysis showed that the TAIs (see Materials and methods) in the PMd and the PCu were significantly greater than zero, suggesting that activities in the PMd and the PCu were more specific in operation than memory (Fig. 3D). The statistical parametric maps and the TAI analysis suggest that, while the PMd, the PCu and the LPs show mental operation-related activities, the activities in the PMd and the PCu are much more specifically related to the mental operation.

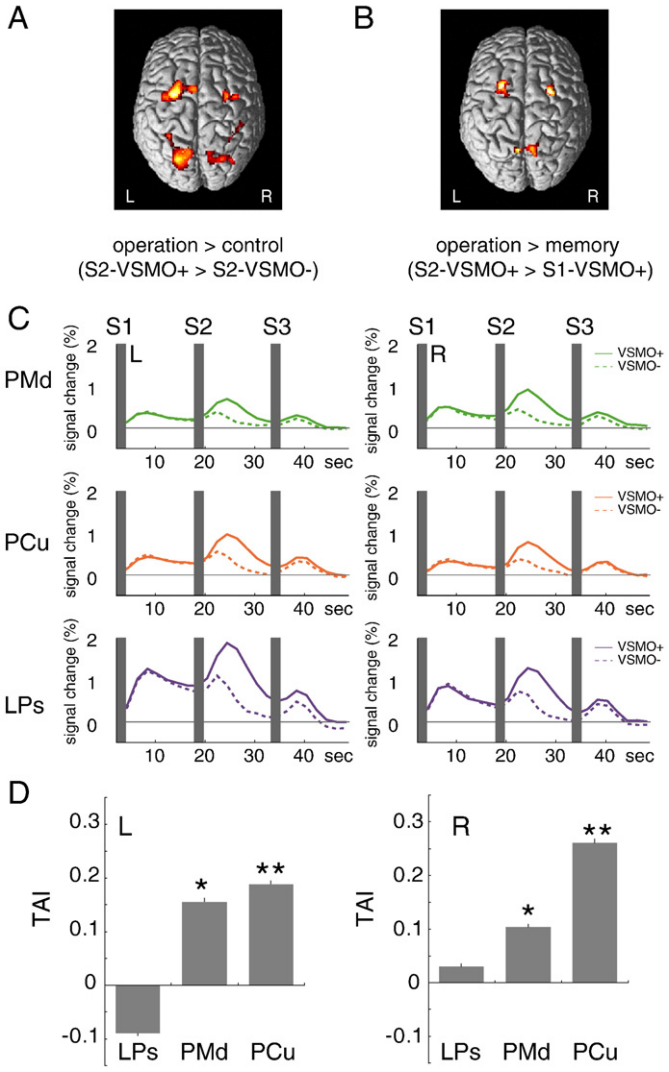

Fig. 3. Brain areas activated in the mental operation task. A. Brain areas activated more in response to S2 in VSMO+ than S2 in VSMO− (operation > control). B. Brain areas activated more in response to S2 in VSMO+ than S1 in VSMO + (operation > memory). The voxel-wise threshold was set at $p<0.05$ corrected for multiple comparisons, with an extent threshold of 50 contiguous voxels. C. Mean time course of the percent signal increase of the PMd, the PCu and the LPs (L, left hemisphere; R, right hemisphere) of all subjects during VSMO+ and VSMO− (green, orange and violet represent PMd, PCu and LPs, respectively. Solid and dotted lines represent VSMO+ and VSMO−, respectively). The MNI coordinate for each area was defined by the activation map of "operation > control (S2+VSMO+ > S2-VSMO−)" shown in A for LPs and "operation > memory (S2-VSMO+ > S1-VSMO+)" shown in B for PMd and PCu: $x=26$, $y=2$, $z=58$ for right PMd; $x=10$, $y=-58$, $z=56$ for right PCu; $x=24$, $y=-72$, $z=48$ for right LPs; $x=-26$, $y=4$, $z=50$ for left PMd; $x=-10$, $y=-62$, $z=54$ for left PCu; and $x=-20$, $y=-72$, $z=54$ for left LPs. D. TAIs for each area (L, left hemisphere; R, right hemisphere). TAIs were calculated from data in VSMO+ (see Materials and methods). In both hemispheres, the TAIs in the PMd and the PCu were significantly greater than zero, indicating that the activities in these areas are more specific for S2-VSMO+ than S1-VSMO+. *$p<0.05$, **$p<0.01$.

Table 1
Mean MNI coordinates for the center of the targeted three locations across subjects for the TMS experiment.

	Mean coordinates ± SD (mm)		
	x	*y*	*z*
PMd	27 ± 3	7 ± 5	62 ± 6
PCu	5 ± 2	−56 ± 5	51 ± 3
LPs	19 ± 5	−67 ± 6	57 ± 6

The actual stimulation locations were determined based on the peak activation in each region individually defined in the fMRI experiment without anatomical normalization. Listed coordinates (*x*, *y*, *z*, based on the Montreal Neurological Institute template) were calculated by means of anatomical normalization. PMd, dorsal premotor cortex; PCu, precuneus; LPs, lateral superior parietal lobule.

TMS experiment

We applied double-pulse TMS with 100 ms ISI to the PMd and the PCu. The aim of the TMS study was to dissociate the characteristics of the two areas that showed simultaneous and specific activation in response to the mental operation cue (S2-VSMO+). We also applied TMS to the LPs that also showed mental operation-related activities, though the temporal character of the LPs' activity was not specific to S2-VSMO+.

The stimulation region was defined based on the fMRI experiment for each subject. Mean coordinates of the stimulated regions were broadly consistent across subjects (Table 1). Grand mean (±SE) accuracy and RT of the VSMO− and VSMO+ task without real stimulation, were 98.3 ± 0.3%, 86.7 ± 1.3%, 737 ± 10 ms and 2025 ±

Table 2
The effect of TMS on ΔRT (ms).

	ΔRT		Two-way ANOVA: *F*-values		
	VSMO+	VSMO−	Area	Task	Area × task
−1500 ms					
PM	80.8 ± 68.5	−9.3 ± 13.1	0.52	0.09	1.52
PCu	−36.1 ± 53.0	2.3 ± 27.7			
LPs	−2.3 ± 45.4	22.2 ± 17.4			
−500 ms					
PM	−44.4 ± 32.0	21.3 ± 15.7	1.09	2.08	0.28
PCu	−119.9 ± 80.3	−17.0 ± 16.9			
LPs	−62.9 ± 66.4	−14.0 ± 20.1			
+300 ms					
PM	155.4 ± 60.0	69.9 ± 25.6	5.78[a]	2.22	6.86[b]
PCu	−100.6 ± 43.3	90.1 ± 36.1			
LPs	8.6 ± 39.7	11.3 ± 16.9			
+500 ms					
PM	11.0 ± 49.6	18.3 ± 18.3	2.36	0.77	1.56
PCu	144.9 ± 112.1	6.9 ± 12.0			
LPs	−70.0 ± 42.2	−53.0 ± 36.9			

RT in the TMS condition minus those in the sham conditions were calculated (ΔRT). Stimulation timings, −1500 ms, −500 ms, +300 ms and +500 ms indicate TMS at 1500 ms before, 500 ms before, 300 ms after and 500 ms after the onset of S2, respectively. VSMO+, the mental operation task; VSMO−, the control task. PMd, dorsal premotor cortex; PCu, precuneus; LPs, lateral superior parietal lobule.

[a] $p<0.05$.
[b] $p<0.01$.

Table 3
The effect of TMS on ΔAccuracy (%).

	ΔAccuracy		Two-way ANOVA: *F*-values		
	VSMO+	VSMO−	Area	Task	Area × task
−1500 ms					
PM	2.5 ± 2.8	0.6 ± 1.5	0.22	0.53	2.84
PCu	−3.8 ± 4.2	3.1 ± 1.9			
LPs	0.0 ± 3.4	1.3 ± 0.8			
−500 ms					
PM	3.1 ± 3.1	3.1 ± 1.7	2.33	3.47	1.78
PCu	8.8 ± 3.4	0.0 ± 0.9			
LPs	0.6 ± 2.5	−0.6 ± 0.6			
+300 ms					
PM	−6.3 ± 3.1	−0.6 ± 1.1	3.64[a]	0.41	4.02[a]
PCu	6.3 ± 3.6	0.0 ± 1.3			
LPs	−3.8 ± 3.4	0.6 ± 1.1			
+500 ms					
PM	−3.8 ± 2.1	−0.6 ± 0.6	3.86[a]	0.17	2.06
PCu	0.0 ± 3.6	−0.6 ± 1.1			
LPs	5.6 ± 2.2	1.3 ± 1.3			

Accuracy in the TMS condition minus those in the sham conditions were calculated (ΔAccuracy). Stimulation timings, −1500 ms, −500 ms, +300 ms and +500 ms indicate TMS at 1500 ms before, 500 ms before, 300 ms after and 500 ms after the onset of S2, respectively. VSMO+, the mental operation task; VSMO−, the control task. PMd, dorsal premotor cortex; PCu, precuneus; LPs, lateral superior parietal lobule.

[a] $p<0.05$.

60 ms, respectively (calculated over all sham trials). The effects of TMS on accuracy and RT were examined by using sham control data, ΔAccuracy and ΔRT.

Since the TAI analysis in the fMRI study showed that the activities in the PMd and the PCu just after the S2-VSMO+ were significantly greater than those after the S1-VSMO+, we had an a priori hypothesis that the effect of the TMS is different depending on the stimulation timing. Two-way ANOVA [area (PMd/PCu/LPs) and task (VSMO+/VSMO−)] revealed a significant interaction between area and task in both ΔRT and ΔAccuracy (ΔRT, $F_{(2,\ 18)}=6.86$; $p=0.006$; ΔAccuracy, $F_{(2,\ 18)}=4.02$; $p=0.036$) only when TMS was applied 300 ms after the onset of S2 (Tables 2 and 3). This indicates that the TMS effect at the timing on the performance of the VSMO+ and the VSMO− was different for each brain area. In this stimulation timing, one-way ANOVA showed that the effect of TMS during VSMO+ was different among areas for both ΔRT and ΔAccuracy (ΔRT, $F_{(2,\ 18)}=6.95$, $p=0.006$; ΔAccuracy, $F_{(2,\ 18)}=4.36$, $p=0.029$; Figs. 4A left and 4B left, respectively). Post-hoc tests for ΔRT revealed that TMS of the PMd (PMd-TMS) and the PCu (PCu-TMS) in VSMO+ produced opposite effects ($p=0.03$, Bonferroni's multiple-comparison test). In fact, compared with baseline, PMd-TMS significantly prolonged RTs whereas PCu-TMS shortened them (PMd, $p=0.029$; PCu, $p=0.045$, one-sample *t*-test). This differential effect of TMS on RTs was considered to be specific to the VSMO+ because such a differential effect was not observed in the VSMO− (Fig. 4A, right). Furthermore, post-hoc tests for ΔAccuracy also showed opposite effect of PM-TMS and PCu-TMS in VSMO+ ($p=0.04$, Bonferroni's multiple-comparison, Fig. 4B, left). The inhibitory effect of PMd-TMS and the facilitatory effect of PCu-TMS stimulation, without any speed-accuracy trade-off, were confirmed by multivariate analysis of variance using Pillai's trace statistic ($F_{(2,\ 17)}=8.44$, $p=0.003$, Fig. 4C). LPs-TMS for this timing showed no significant effect.

For other stimulation timings, two-way ANOVA showed no significant interaction between area and task. Furthermore, one-way ANOVA showed no significant differences between areas.

Discussion

The present fMRI experiment revealed that, of the fronto-parietal areas, the PMd and the PCu were specifically activated in the visuospatial mental operation process. We then identified the segregated involvement of the PMd and the PCu in visuospatial mental operations using TMS. Consequently, PMd-TMS inhibited the task performance, whereas PCu-TMS facilitated it. This suggests that the PMd and the PCu are differentially involved in the visuospatial mental operation process.

PMd-TMS significantly slowed RTs in both VSMO− and VSMO+. Since RTs in VSMO+ include both motor (i.e., reaction) and cognitive components (i.e., mental operation), TMS can disrupt both of them. Considering that the motor component of the reaction in VSMO− and VSMO+ is the same and that the effect of PMd-TMS in the VSMO+ task was much stronger than those in VSMO−, the results indicate that PMd-TMS disrupted not only the motor component but also the cognitive component in VSMO+. Thus, we consider that PMd-TMS in VSMO+ also inhibits the visuospatial mental operation behavior. This

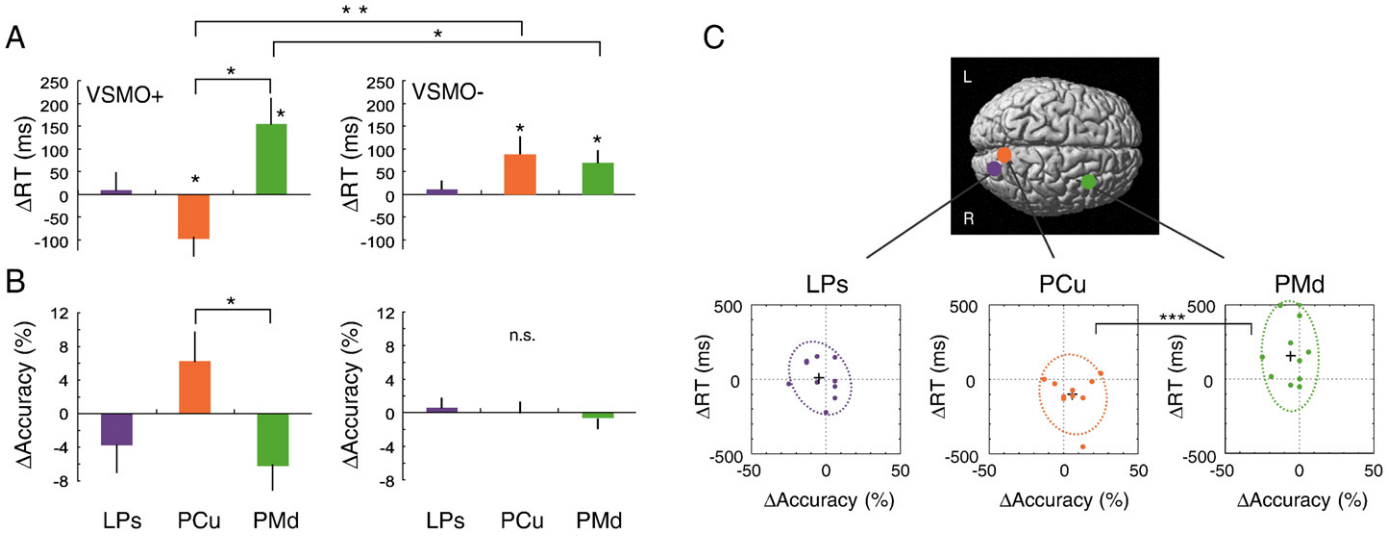

Fig. 4. A. The mean effect of TMS at 300 ms after the onset of S2 on reaction time (ΔRT, error bar = ±SEM). B. The mean effect of TMS at 300 ms after the onset of S2 on accuracy (ΔAccuracy, error bar = ±SEM). The effects of TMS on both ΔRT and ΔAccuracy after stimulation of the PMd or the PCu were significantly different and opposite in VSMO+, while, in VSMO−, neither ΔRT nor ΔAccuracy showed any difference. Note that, though PMd-TMS and PCu-TMS showed a significant effect on ΔRT in both VSMO+ and VSMO− (one-sample *t*-test), the effects of PMd-TMS and PCu-TMS in VSMO− were much lower than those of VSMO+, respectively (paired *t*-test). *$p<0.05$, **$p<0.01$ C. Plots of ΔRT and ΔAccuracy for each subject (dotted lines are 95% confidence ellipses). ***$p<0.005$.

finding is supported by a previous report showing that repetitive TMS of the PMd disrupted a visuospatial mental operation (Tanaka et al., 2005). This inhibition of the performance by PMd-TMS in VSMO+ supports a suggestion from previous evidence that the PMd would be involved in the executive processing of the visuospatial mental operation. Studies in non-human primates have reported that neurons in the PM are specifically activated during observation of well-learned motor tasks or during conversion of memorized information into a motor sequence (direction and order) before its execution (Cisek and Kalaska, 2004; Ohbayashi et al., 2003; Seidler et al., 2004). These observations suggest that the PM contributes to the internal generation of action sequences. A recent fMRI study showed that sequencing functions of the PMd can be applied to a non-motor cognitive operation (Abe et al., 2007). Taken together, we suggest that the PMd plays an executive role in the present mental operation task in which an internally simulated operation sequence, once completed, generates a single path and directs the subjects straight to the goal.

PCu-TMS did not inhibit performance while the fMRI signal in this region specifically increased in response to the operation cue. Many studies have shown that damage that includes the medial parietal area disrupts the ability to adapt self-position to target position in visuomotor control (Galletti et al., 1997; Galletti et al., 2003). The self-monitoring function of the medial PPC has also been suggested based on studies of navigation (Ghaem et al., 1997; Sato et al., 2006; Takahashi et al., 1997). As is well-known for the motor control domain, the feedback monitoring system functions to precisely correct movements when they are inaccurate by comparing the target position and the predicted movement end-position according to a copy of the movement command (efferent copy) and sensory inflow (Desmurget and Grafton, 2000). In contrast, unlike such target-directed action with precise control of the action, the present task did not require subjects to perform a target-directed behavior but instead required subjects to internally generate the operation path in accordance with the rule by tracing the memorized line pattern. In addition, precise control of line tracing was not necessary to achieve the task. Thus, providing the internal operation path can be generated in a rule-based manner by the executive of the operation, one can reach the goal and achieve the task even if the monitoring function is impeded to some extent. Taken together, we suggest that the reason why interference of the PCu by TMS did not disrupt the task performance can be explained by the combination of the characteristics of the present task and the involvement of the PCu for “feedback” monitoring. To clarify the relevance of the monitoring functions of the PCu, the TMS effect on the PCu must be examined by using, for example, a visuospatial mental operation task in which the necessity of monitoring is parametrically-controlled.

An unexpected outcome of this study was that PCu-TMS shortened RTs with a tendency towards improved accuracy. One possible explanation is inter-sensory facilitation by the sound or electrical stimulation generated by TMS (Nickerson, 1973; Terao et al., 1997). However, the explanation of a nonspecific effect of TMS is unlikely because the facilitation was specific to the brain-region and time. In other words, the shortening of RTs occurred only when TMS was delivered to the PCu at 300 ms after the onset of the operation cue (S2 in VSMO+). Therefore, it is reasonable to believe that the observed facilitation was due to the effects of TMS on the underlying cortical regions. Another possible explanation is that mental resources were released to other activities relevant to task performance by inhibiting redundant functions. As noted above, although subjects must trace lines, precise tracing was not necessary. Thus, we suggest that the PCu, which is likely to be involved in the monitoring of line tracing and evoked regardless of its relevancy, may in fact be redundant or not critical to the task. If this is the case, inhibition of the activities of the PCu might release the resource and facilitate task performance. This idea is consistent with a report of patients with parietal lesions who failed to match imagined and actual pointing movements and, instead, achieved the imaginary movements with abnormally high performance speeds without influence from the target size (Sirigu et al., 1996). Such paradoxical functional improvements have also been supported by TMS studies (Hilgetag et al., 2001; Kobayashi et al., 2004). For example, inhibition of the unilateral motor cortex by 1 Hz repetitive TMS, resulted in the improvement of finger movements ipsilateral to the stimulated hemisphere, probably because the transcortical inhibition between the motor cortices was also suppressed (Kobayashi et al., 2004). Nevertheless, the event-related TMS used in the present study would not exactly induce the same effect as repetitive TMS and would not make subjects act like patients. To confirm this idea, additional experiments using the twin-coil TMS method (Koch et al., 2008; Sack et al., 2005), for example, that can test both the functional and anatomical connections between the PMd and the PCu, will be required.

Considering that the RTs of VSMO− (a type of choice reaction task) and those of VSMO+ in the TMS study were ca. 700 and 2000 ms, respectively, the mental operation may be achieved during the 1300 ms period after the onset of the operation cue (S2 in VSMO+). However, only TMS at 300 ms after the onset of the operation cue significantly affected the task performance, while TMS at 500 ms after the onset of the cue showed no effect. The results suggest that the initial 300 ms period after the cue onset is critical for neural activities related to the mental operation processes. On the other hand, there is the possibility that the stimulation intensity used here was not enough to impede neural activities 500 ms after the onset of the cue. There is also the possibility that the TMS effect was not time-locked to the areas' temporal activities during VSMO. In the present study, we examined the TMS effect of only four time windows in the task because we had to minimize the total number of trials from the aspect of the protection of the subjects. To reveal the detailed temporal specificities of the PMd and the PCu during the visuospatial mental operation, the effect of TMS on other time windows should be examined in future studies.

Since the stimulated site for the PMd-TMS is close to areas related to overt eye movement, such as the frontal eye field (Paus, 1996), there is a possibility that the TMS effect might be due to interference with eye movements. However, to prevent overt eye movement in the present study, we asked subjects not to move their eyes. All stimuli were presented in the center of the screen and their size was small (2° or less). Furthermore, a visuospatial pattern was (very) briefly presented (500 ms) and masked. Thus, we consider that subjects internally performed the task without significant overt eye movement and the TMS affected the neural activities of the visuospatial mental operation. Even if that is the case, it is difficult to completely exclude the possibility because previous reports have suggested that eye movements contribute to the mental imagery process and might be tightly linked with visuospatial mental operations (Brandt and Stark, 1997; Mast and Kosslyn, 2002).

The LPs showed strong fMRI activities during the mental operation task with non-specificity to the cues (memory/operation). On the other hand, TMS of this area showed no effect at any stimulation time. One possibility is that this area might not be critically involved in the processing of the task. It is also possible that the stimulation intensity and/or duration might not be sufficient to induce meaningful behavioral change in the task. Although the exact function of the LPs in the mental operation remains to be clarified, considering that LPs are implicated in working memory-related functions such as memory retention, visual imagery or memory retrieval (Formisano et al., 2002; Hanakawa et al., 2003c; Sack et al., 2002) and that such functions may be continuously and basically active during the visuospatial mental operation, the LPs' activities found in the present task appear to represent such memory-related functions. Another possibility is that the LPs might have an important role at other time points of the mental operation. In the experiment, the TMS was delivered only 1500 or 500 ms before or 300 or 500 ms after the onset

of the operation cue. Therefore, if the TMS was delivered to the LPs earlier than 1500 ms before or later than 500 ms after the onset of the operation cue, an interference effect may be observed.

We conclude that, although both the PMd and the PCu are specifically activated during visuospatial mental operations, these two areas are differentially involved in the visuospatial mental operation process. The PMd is involved in generating an operation path as an executive of the mental operation, whereas the PCu is involved in other supportive functions such as monitoring of the operation with reference to the internally represented visual image.

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