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Hemispheric Asymmetry in Memory-Guided Pointing During Single-Pulse Transcranial Magnetic Stimulation of Human Parietal Cortex

Michael Vesia,^{1,2,4} Jachin A. Monteon,^{1,2,5} Lauren E. Sergio,^{2,3,4} and J. D. Crawford^{1,2,3,4,5}

¹Canadian Institutes of Health Research Group on Action and Perception, ²Centre for Vision Research and ³Departments of Psychology, ⁴Kinesiology and Health Science, and ⁵Biology, York University, Toronto, Canada

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Vesia, Michael, Jachin A. Monteon, Lauren E. Sergio, and J. D. Crawford. Hemispheric asymmetry in memory-guided pointing during single-pulse transcranial magnetic stimulation of human parietal cortex. *J Neurophysiol* 96: 3016–3027, 2006. First published September 27, 2006; doi:10.1152/jn.00411.2006. Dorsal posterior parietal cortex (PPC) has been implicated through single-unit recordings, neuroimaging data, and studies of brain-damaged humans in the spatial guidance of reaching and pointing movements. The present study examines the causal effect of single-pulse transcranial magnetic stimulation (TMS) over the left and right dorsal posterior parietal cortex during a memory-guided “reach-to-touch” movement task in six human subjects. Stimulation of the left parietal hemisphere significantly increased endpoint variability, independent of visual field, with no horizontal bias. In contrast, right parietal stimulation did not increase variability, but instead produced a significantly systematic leftward directional shift in pointing (contralateral to stimulation site) in both visual fields. Furthermore, the same lateralized pattern persisted with left-hand movement, suggesting that these aspects of parietal control of pointing movements are spatially fixed. To test whether the right parietal TMS shift occurs in visual or motor coordinates, we trained subjects to point correctly to optically reversed peripheral targets, viewed through a left–right Dove reversing prism. After prism adaptation, the horizontal pointing direction for a given visual target reversed, but the direction of shift during right parietal TMS did not reverse. Taken together, these data suggest that induction of a focal current reveals a hemispheric asymmetry in the early stages of the putative spatial processing in PPC. These results also suggest that a brief TMS pulse modifies the output of the right PPC in motor coordinates downstream from the adapted visuomotor reversal, rather than modifying the upstream visual coordinates of the memory representation.

INTRODUCTION

The posterior parietal cortex (PPC) is critical for spatial processing and visually guided action (Andersen et al. 1997; Colby and Goldberg 1999; Goodale and Milner 1992; Jeannerod et al. 1995). Primate neurophysiology has identified a number of parietal areas within the intraparietal sulcus that process information for specific visuomotor functions (Andersen and Buneo 2002; Colby and Goldberg 1999). In particular, the lateral intraparietal area (LIP) codes the location of targets for eye movements termed saccades (Dickinson et al. 2003; Snyder et al. 1997), whereas the parietal reach region (PRR)—an area in the medial aspect of the posterior parietal cortex—is specialized for planning target-directed limb movements (Batista et al. 1999; Calton et al. 2002). Both areas are thought to encode this information in contralateral space rela-

tive to a gaze-centered, eye-fixed frame of reference (Batista et al. 1999; Colby et al. 1995; Duhamel et al. 1992; Stricanne et al. 1996).

Recent functional magnetic resonance imaging (fMRI) revealed a similar functional organization in PPC of humans that includes areas specialized for saccades (LIP) (Medendorp et al. 2003, 2005; Schluppeck et al. 2005; Sereno et al. 2001) and reaching (PRR) (Connolly et al. 2003; DeSouza et al. 2000; Medendorp et al. 2003, 2005) toward targets in the contralateral visual field. More recently, a similar region was identified when reaching toward central and peripheral visual targets (Prado et al. 2005). Further evidence implicating the PPC in movement planning comes, in part, from examining deficits in patients with damaged cerebral cortex. For instance, lesions of PPC, centered on the parietal-occipital junction in humans (Karnath and Perenin 2005), result in a specific deficit of visually guided behavior referred to as optic ataxia, characterized by visually guided errors to targets in the contralateral visual field that are not attributed to a solely motor or visual perturbation (Battaglia-Mayer and Caminiti 2002; Jakobson et al. 1991; Perenin and Vighetto 1988; Rossetti et al. 2003). In addition, both functional imaging and patient investigations have shown that the PPC contains a dynamic internal spatial representation that updates contralateral space in a gaze-centered frame of reference when the eyes rotate (Khan et al. 2005a,b; Medendorp et al. 2003; Merriam et al. 2003).

Nevertheless, functional neuroimaging techniques, such as fMRI, allow identification of the brain regions correlated with a given behavior only, whereas inferences from patient studies are limited by highly variable lesions and do not take into account the inherent compensatory plasticity of the brain after the insult. In contrast, transcranial magnetic stimulation provides a methodology for determining the causal inferences with respect to the relationship between neural processes in specified brain areas and normal behavior (Jahanshahi and Rothwell 2000; Pascual-Leone et al. 1999, 2000; Robertson et al. 2003; Walsh and Cowey 2000). In particular, TMS studies in humans provide evidence for critical involvement of PPC in several areas of visuomotor control including the programming and execution of saccades (Elkington et al. 1992; Kapoula et al. 2001, 2004, 2005; Muri et al. 1996, 2000; Nyffeler et al. 2005; Oyachi and Ohtsuka 1995; Tzelepi et al. 2005; Yang and Kapoula 2004), eye–hand interactions (van Donkelaar and Adams 2005; van Donkelaar et al. 2000), and the on-line

Address for reprint requests and other correspondence: J. D. Crawford, York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3 (E-mail: jdc@yorku.ca).

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control of reaching (Desmurget et al. 1999) and grasping (Glover et al. 2005; Tunik et al. 2005).

However, few studies to date have used the disruptive effect of TMS to probe the functional relevance of the parietal cortex for spatial representation during a memory-guided pointing movement. Perhaps the only exception was that of Smyrnis et al. (2003), who showed that the application of single pulses of TMS over PPC during the memory period disrupts the early stages of encoding a spatial location while moving a cursor across the surface of a workspace in the horizontal plane to a given remembered target displayed on a computer monitor screen in the vertical plane. This disruption was manifested by an increase in the variance of pointing precision in both visual fields, but only during TMS to the left PPC. Surprisingly, TMS to the right PPC had no significant effect.

Although the findings of Smyrnis et al. (2003) suggest an involvement of the PPC in early control of memory-guided pointing, several questions remain. In particular, why was there only increased scatter during left PPC TMS, and why was there no sign of the direction-specific contralateral organization observed in fMRI and patient studies? One possibility is that Smyrnis et al. (2003) used an indirect mouse-pointing transformation rather than a natural reach directly to the spatial target (Gorbet et al. 2004; Messier and Kalaska 1997). Another possibility is that the authors used a standard 9-cm-diameter circular coil, which may not provide an optimally focal means of brain stimulation with TMS, compared with the more recently popular figure-of-eight coil (Pascual-Leone et al. 1999; Robertson et al. 2003).

Here, we address these issues by using a figure-of-eight coil to deliver single-pulse TMS to transiently disrupt the putative processing within the dorsal PPC of both hemispheres during a memory-guided "reach-to-touch" movement directly to the spatial location of the visual target. Our results from *Experiment 1A* confirm that TMS to left PPC produces a specific increase in pointing scatter. However, we also found that during right parietal stimulation, the directional error of pointing movements systematically shifted leftward in both visual fields.

In *Experiment 2*, we further investigated the latter systematic leftward shift with the use of a recently developed visuomotor adaptation paradigm (Marotta et al. 2005). A recent fMRI study suggests that after reversing prism adaptation, PPC activity remains tied to the reversed visual input rather than the direction of motor output (Fernandez-Ruiz et al. 2004). We similarly reasoned that, if any left-right TMS shift was elicited within a visual coordinate frame in the brain, the pointing errors would remain fixed in visual coordinates, that is, reversing vision would reverse the behavioral errors left to right. However, if the neural bias originated in motor coordinates, the behavioral errors should not be affected by the reversal of vision. The aim of this second experiment was to investigate whether these pointing movements remain fixed in visual coordinates—similar to results observed using fMRI—or motor coordinates after reversing prism adaptation during stimulation of the right dorsal PPC.

METHODS

Subjects

Six human subjects (three males and three females, aged 20–30 yr) provided written informed consent before inclusion. All participants

were right-handed, as defined by the Edinburgh Inventory of Manual Preference (Oldfield 1971), in good health, and, according to a self-report, without any known neurological or muscular deficits. All experimental procedures received ethical approval by the York Human Participants Review Subcommittee.

Apparatus

The experimental device was the same in all conditions and consisted of a modular chin-rest/prism assembly fixed to a horizontal tabletop surface in front of a liquid crystal display (LCD) screen (Marotta et al. 2005). Briefly, the prism assembly consisted of opaque goggles in which a removable left-right reversing Dove prism ($12.5 \times 3 \times 3$ cm) was mounted in a black Plexiglas frame 40 cm from a LCD screen that allowed monocular vision in the right eye, and a chin rest that fixed the subject's head and aligned the eye with the central fixation cross. Stimuli were presented at one of four different locations in the periphery (2.3° left, 4.6° left, 2.3° right, 4.6° right relative to the central fixation cross). These target positions corresponded to locations on the vertical screen of 16 and 32 mm from the central fixation cross on the left visual field (LVF, signed negative) and the right visual field (RVF, signed positive), respectively. All of the stimuli were restricted to a 14×11.5 -cm window so that the central fixation cross (15 cm from the left edge of the LCD screen) fell at the center of the prism view (Fig. 1, *B* and *C*). This setup allowed for visual feedback of the hand briefly at the end of the movement and was necessary for the second experiment. A caveat of this setup was that eye movements could not be monitored on-line.

To verify that subjects were able to maintain central fixation during the task, we performed a control study where eye position was monitored using an eye-tracking system (Applied Science Laboratories, Bedford, MA) for both nonstimulation and stimulation conditions during the memory interval and execution epochs. Results confirmed that subjects could maintain central fixation throughout the experiment.

Pointing movements were monitored by two OPTOTRAK three-dimensional (3-D) motion-tracking systems (Northern Digital, Waterloo, Ontario, Canada), which recorded three 8-mm-diameter infrared light-emitting diodes (IREDs), attached to the distal portion of the subject's left or right index fingertip. The starting hand position was aligned with the central fixation cross but positioned 13 cm below it in the frontal plane and placed on a table surface in the horizontal plane 10 cm away from the subject's torso. The two-dimensional (2-D) coordinates of the IREDs were recorded at a rate of 200 Hz and stored on hard disk for off-line analysis.

TMS protocol

Single-pulse TMS was delivered using a MagStim 200 magnetic stimulator (MagStim, Whitland, UK) and a 70-mm figure-of-eight coil. Custom software triggered the magnetic stimulator 250 ms after the peripheral target extinguished during the memory delay period for the stimulation conditions (see *Experimental procedure*). It was previously suggested that motor threshold is not an appropriate measure of individual magnetic stimulus intensity in nonmotor areas of the brain because of the lack of correlation between motor and phosphene thresholds in healthy normal subjects (Boroojerdi et al. 2002; Stewart et al. 2001). Accordingly, the intensity of magnetic stimulation was fixed to 60% of the stimulator output (Beckers and Zeki 1995; Corthout et al. 1999; Dambeck et al. 2006; Lewald et al. 2002). All stimulation parameters were in accordance with the safety guidelines for magnetic stimulation (Wassermann 1998). For anatomic reference, locations for TMS coil placement were determined according to the 10–20 EEG (electroencephalogram) coordinate system (Herwig et al. 2003) and confirmed a posteriori by MRI using vitamin E capsules as markers of stimulated skull positions (Fig. 1A). Commercially available 10–20 EEG stretch caps for 20 channels (Electro-Cap Interna-

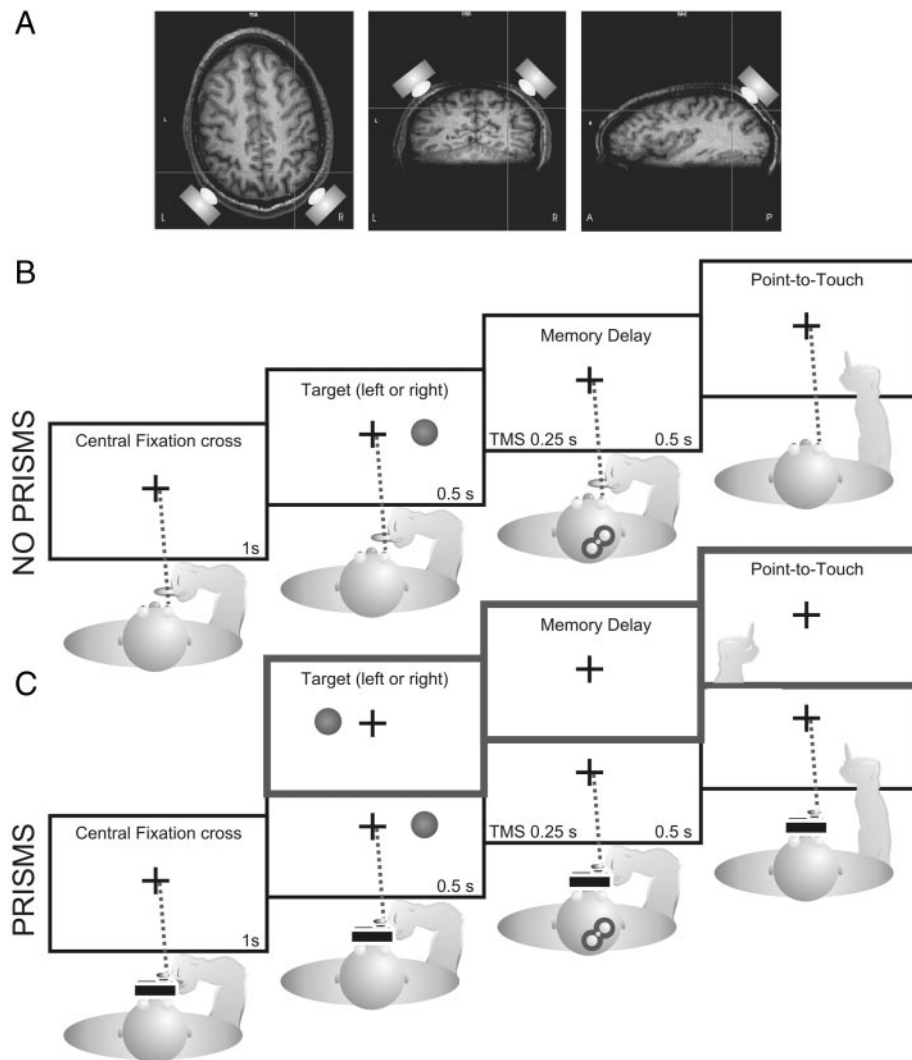


FIG. 1. *A*: location of individual transcranial magnetic stimulation (TMS) sites for one representative subject. Stimulation sites are shown in the left and right posterior parietal cortex with the position of high-intensity signal markers placed on the subject's skull (P3 and P4, respectively). Gray bars indicate position of the TMS coil. Stimulation sites were verified a posteriori using the magnetic resonance imaging (MRI) of the individual subject. Anatomical site of stimulation for right posterior parietal cortex (PPC, shown here) is indicated by the line intersection in the transverse (leftmost panel) coronal (middle panel), and sagittal (rightmost panel) sections of T1-weighted MRI. *B*: delayed-pointing task. Subjects fixated a central cross for 1 s. Then a peripheral dot was presented toward the left or right of fixation. After this pointing target extinguished, a brief TMS pulse was delivered (0.25 s thereafter, on TMS trials only) during a 0.5 s memory-delay period. At this point, subjects were signaled by an auditory tone to perform a rapid pointing movement to the remembered target location and then immediately return to the start position. Time between successive movements was 5 s. *C*: viewpoint from the subject's perspective. Prism-pointing task was identical to the previous task except that the subject had to point while looking through a left-right Dove reversing prism. When looking through the prism, the subject's view of the pointing hand and the actual movement appeared to be reversed. This reversed view of the pointing target caused subjects to adapt their pointing movements to the opposite direction. Top row of boxes is a rendering of the subject's view through the prism.

tional, Eaton, OH) were used to define the 10–20 EEG positions. The cap sizes were selected according to the individual head size and fitted to the subjects' heads. The putative vector of the magnetic current was derived by virtually prolonging the orthogonal to the line tangent to the skull at the stimulation site by 15 mm from the scalp onto the cortical surface of the structural MRI by means of Brain Voyager 4.6 software (Brain Innovation, Maastricht, The Netherlands). This cortical site then was identified in the Talairach atlas (Talairach and Tournoux 1988) and the corresponding coordinates and anatomical and Brodmann areas of stimulation were obtained. Specifically, MRI showed that test locations overlay left and right dorsal PPC (P3 and P4, respectively) and included the intraparietal sulcus, Brodmann area 19, and the adjacent cortex in the superior and inferior parietal lobule. Across subjects, the average Talairach coordinates (in millimeters) and their SDs approximately were $x = -39$ (6), $y = -68$ (5), $z = 38$ (6) on the left hemisphere and $x = 36$ (1), $y = -73$ (6), $z = 41$ (4) on the right hemisphere.

Two additional control experiments were conducted to yield estimates of nonspecific effects of TMS on both testing days (i.e., both left and right hemispheric stimulation had their own control conditions). First, we assessed performance after stimulation of the vertex (Cz). Second, we conducted "sham" trials in which the coil was held close to the subject's skull, but angled away so that no current was induced in the brain. None of the subjects reported any undesirable side effects as a result of the stimulation.

Experimental procedure

Left and right hemispheric stimulation were performed on separate days to minimize fatigue and TMS exposure for each session. Subjects first underwent right hemispheric stimulation, while reaching with the right hand, and then returned the following week for left hemispheric stimulation (*Experiment 1A*). A follow-up experiment (*Experiment 1B*), stimulating both the left and right hemispheres (counterbalanced), was then performed to investigate whether the pointing asymmetry remained spatially fixed or reversed with left-hand movement. In *Experiment 1* (Fig. 1*B*), subjects performed a baseline task in which they pointed to peripheral targets under open-loop conditions. At the start of each experimental trial, a fixation cross appeared for 1,000 ms. A peripheral target (0.5° circle) then briefly appeared for 500 ms to either the left or right of this fixation cross at random horizontal eccentricities between 2.3 and 4.6°. A single-pulse TMS was delivered 250 ms after this peripheral target extinguished (on TMS trials only) during the 500 ms memory delay period. Based on a preliminary experiment, this early stimulation time during the memory delay had the most significant effect on the subsequent accuracy of pointing movements and is consonant with a previous finding (Smyrnis et al. 2003). After the delay period, an auditory tone signaled the subjects to use their dominant right hand (or nondominant left hand in the follow-up experiment) to point to the remembered peripheral target. Subjects were instructed to maintain central fixation of the eyes at all times. In every block, each peripheral target location

was repeated ten times in random order (40 trials) for each of the four stimulus conditions (no stimulation, test stimulation, control stimulation, and “sham” stimulation). Two blocks were collected for the baseline (no TMS with no prism), control (Cz and “sham” TMS with no prism), and test (PPC TMS with no prism) conditions.

For right PPC stimulation with the right hand only (based on results from *Experiment 1A*), subjects then underwent a training session on a separate day while wearing a left–right Dove reversing prism (*Experiment 2*, Fig. 1C). Subjects were considered “trained” once they could successfully perform ten accurate pointing movements consecutively. After learning to correctly point to the optically reversed peripheral targets during the prism training condition, subjects were retested on the pointing task while looking through the reversing prism (test condition). Two blocks were collected for the baseline (no TMS with prism) and right parietal stimulation condition (P4 TMS with prism).

Data analysis

Movement start and end were scored at 5% peak tangential velocity. Pointing accuracy to visual targets was quantified by recording the spatial coordinates in the horizontal (x) and vertical (y) axes of movement endpoints in the frontal plane. Pointing accuracy parameters were assessed by calculating 1) constant error—the mean distance between the fingertip at movement end and each target location and 2) variable error—the distance of the endpoints of each movement from the mean final position (95% confidence ellipses of the scatter of fingertip at movement end). The linear distance between the initial fingertip position and its movement endpoint defined movement amplitude, whereas movement direction was defined as the direction in degrees of this vector (Gordon et al. 1994; Messier and Kalaska 1997).

Ellipses were fit to the 2-D data set in such a way that the horizontal and vertical coordinates of the ellipse corresponded to the mean of the data. The semimajor (principal axis) and semiminor (orthogonal to the

principal axis) axes correspond to the data with the highest and lowest dispersion from the mean, respectively. Based on these axes, confidence ellipses including 95% of the movement endpoint population were constructed (Messier and Kalaska 1997; Sokal and Rohlf 1981). Accordingly, constant error provides a measure of overall accuracy with respect to target position and variable error gives a measure of the global pointing scatter (Revol et al. 2003). Repeated-measures ANOVA and Tukey post hoc tests were used to test the statistical reliability of differences between mean elliptical areas and horizontal errors for movement endpoints; *t*-tests were used to test significance of pointing error direction before and after prism adaptation.

RESULTS

Experiment 1A: TMS during memory-guided pointing with right hand

LEFT PARIETAL TMS. The fixation position was always straight ahead (aligned with midsagittal plane of head), but the pointing targets (●) varied from 32 mm left to 32 mm right of this fixation position. The symbols ● (no stimulation) or □ (parietal stimulation) indicate the 20 individual endpoints for each condition in one typical subject. For illustrative purposes, Fig. 2A depicts pointing performance in 95% confidence interval elliptical fits to these data in the no stimulation (gray ellipses) and left parietal stimulation (black ellipses) conditions only for each of the four pointing targets. Figure 2, B and C shows the mean ellipses of all six subjects superimposed one on top of each other.

In the baseline condition, subjects slightly but systematically overshoot the pointing targets (relative to the central fixation cross) in the horizontal axis for the no stimulation condition

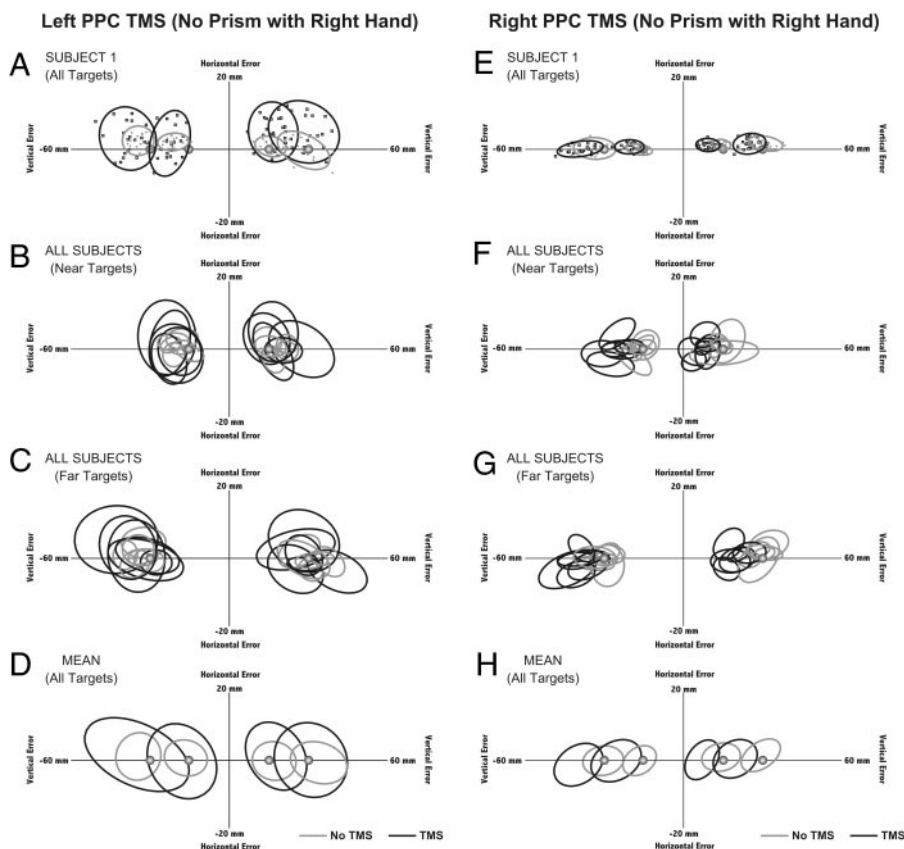


FIG. 2. Mean endpoint confidence ellipses with dominant right hand during the delayed-pointing task for left (*left*) and right (*right*) hemispheric TMS with no prism. Horizontal and vertical axes correspond to the *x*- and *y*-coordinates of the movement endpoints in the frontal plane while subject is fixating the central cross. Four possible pointing targets (●) are shown in eye-centered coordinates from –32 mm right to 32 mm left of fixation. A and E: movement endpoints and their 95% confidence interval elliptical fits for one typical subject in the no stimulation (gray ellipses) and parietal stimulation (black ellipses) conditions. Symbols ● (no stimulation/baseline) or □ (parietal stimulation) indicate the 20 individual endpoints for each condition. B, C, F, and G: ellipses for all 6 subjects superimposed one on top of each other for near (B, F) and far (C, G) targets. D and H: mean elliptical fits for all subjects.

(gray ellipses). These data are consistent with results of previous studies that similarly found this retinal exaggeration effect (Bock 1986; Henriques et al. 1998; Medendorp and Crawford 2002; Poljac and van den Berg 2003; Pouget et al. 2002).

Importantly, endpoint variability (elliptical area) increased in the left PPC stimulation condition (black ellipses) for both near (Fig. 2B) and far targets (Fig. 2C), independent of visual field, compared with the baseline (gray ellipses), as is evident by the stochastically larger pointing errors along the vertical and horizontal axes. However, there was no systematic leftward or rightward shift in the horizontal component of the pointing ellipses for any of the targets. This behavior was consistent for all subjects except for one who showed a smaller range of errors, as shown in the mean elliptical data (Fig. 2D).

To quantify these qualitative observations, we calculated the corresponding areas of the ellipses and separated the horizontal pointing component from the overall pointing performance and analyzed it independently. We then performed two separate two-way repeated-measures ANOVAs, condition (four levels: baseline, sham, control, and parietal stimulation) \times visual field [two levels: left (LVF) and right (RVF)] with respect to variability in pointing (elliptical areas) and mean horizontal pointing error.

Figure 3 illustrates the main finding for left PPC. For illustrative purposes, data are shown separately for both the elliptical areas and horizontal errors to left and right pointing targets. Figure 3, A and B shows the mean elliptical areas for left hemispheric stimulation for each of the four conditions in the LVF (Fig. 3A) and RVF (Fig. 3B). As shown, there was a significant main effect only for condition [$F_{(3,15)} = 16.167$; $P = 0.001$] in elliptical areas. Post hoc analyses (Tukey) showed that left parietal stimulation (P3) significantly increased the elliptical area compared with that in all other experimental conditions (P3 vs. sham, $P = 0.001$; P3 vs. Cz, $P = 0.001$; P3 vs. baseline, $P = 0.001$). In particular, the mean areas of the ellipses for P3 stimulation ($289.67 \pm 60.96 \text{ mm}^2$ for LVF and $227.08 \pm 52.19 \text{ mm}^2$ for RVF) were greater in magnitude compared with baseline and controls (LVF = base-

line: $70.21 \pm 13.31 \text{ mm}^2$; sham: $65.21 \pm 16.16 \text{ mm}^2$; Cz: $67.51 \pm 12.11 \text{ mm}^2$; RVF = baseline: $74.33 \pm 9.16 \text{ mm}^2$; sham: $56.67 \pm 11.46 \text{ mm}^2$; Cz: $67.75 \pm 12.82 \text{ mm}^2$). The pattern of responses was consistent across visual fields as shown by the nonsignificant condition \times visual field interaction [$F_{(3,15)} = 1.797$; $P = 0.191$]. In contrast to the increased elliptical areas (scatter), no significant differences were found in the mean horizontal pointing errors ($P > 0.05$) for left hemispheric stimulation (Fig. 3, C and D), irrespective of condition or visual field.

RIGHT PARIETAL TMS. Figure 2, E–H (right) and Fig. 4 both use the same conventions to show our findings during right PPC TMS. As expected, Fig. 2, E–H qualitatively shows that subjects systematically overshoot the pointing targets in the horizontal axis for the baseline control. However, in this case, there was no increase in the scatter of the ellipses during right parietal stimulation (black ellipses). Instead, the center of the ellipses shifted to the left for all targets in both visual fields compared with the baseline (gray ellipses).

Figure 4 clearly shows that, when compared with left hemispheric stimulation (Fig. 3), the reverse is true for elliptical areas and horizontal pointing error during right hemispheric stimulation. This notion is qualitatively illustrated by Fig. 4, A and B and confirmed quantitatively by statistical analyses indicating that the elliptical areas were not significantly different across the conditions and visual fields ($P > 0.05$). In addition, Fig. 4, C and D shows a significant main effect for condition [$F_{(3,15)} = 44.323$; $P = 0.001$] for the mean horizontal error to left and right targets. Post hoc analyses (Tukey) showed that right parietal stimulation (P4) significantly increased the mean horizontal error compared with that in all other experimental conditions (P4 vs. sham, $P = 0.001$; P4 vs. Cz, $P = 0.001$; P4 vs. baseline, $P = 0.001$). Interestingly, the mean horizontal pointing was systematically biased in the direction contralateral to the hemispheric stimulation site. That is, the directionality of the horizontal pointing error for right parietal stimulation was systematically shifted leftward compared with baseline and controls, independent of visual field

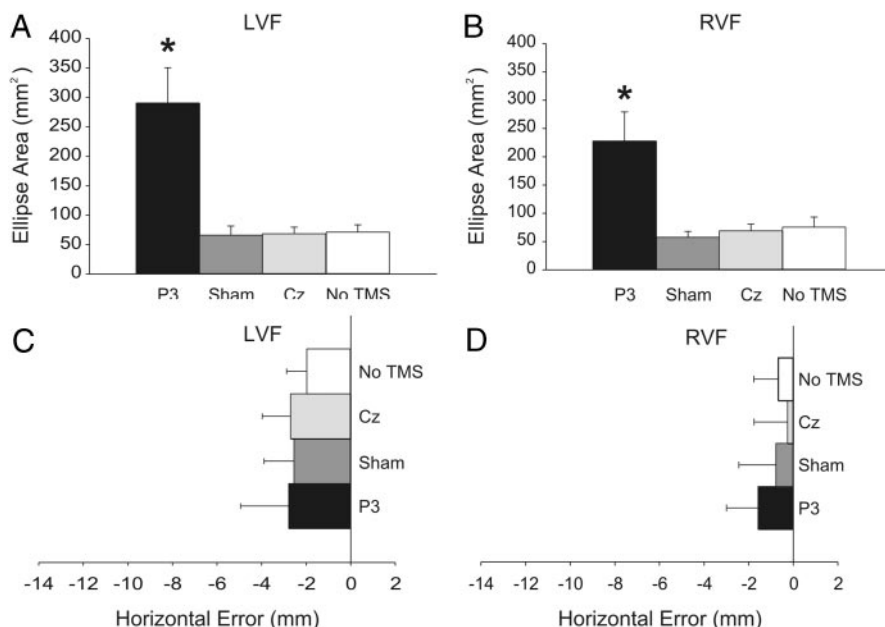


FIG. 3. Mean elliptical areas and horizontal error with dominant right hand in all 4 conditions for left hemispheric TMS with no prism. Mean elliptical areas for left visual field (LVF, A) and right visual field (RVF, B) for all 6 subjects. Mean horizontal error for LVF (C) and RVF (D) for all 6 subjects. Four stimulation conditions: (i) P3 and P4 (left and right parietal, respectively); (ii) “sham” control; (iii) Cz (control site); and (iv) no TMS (baseline). Bars represent SE.

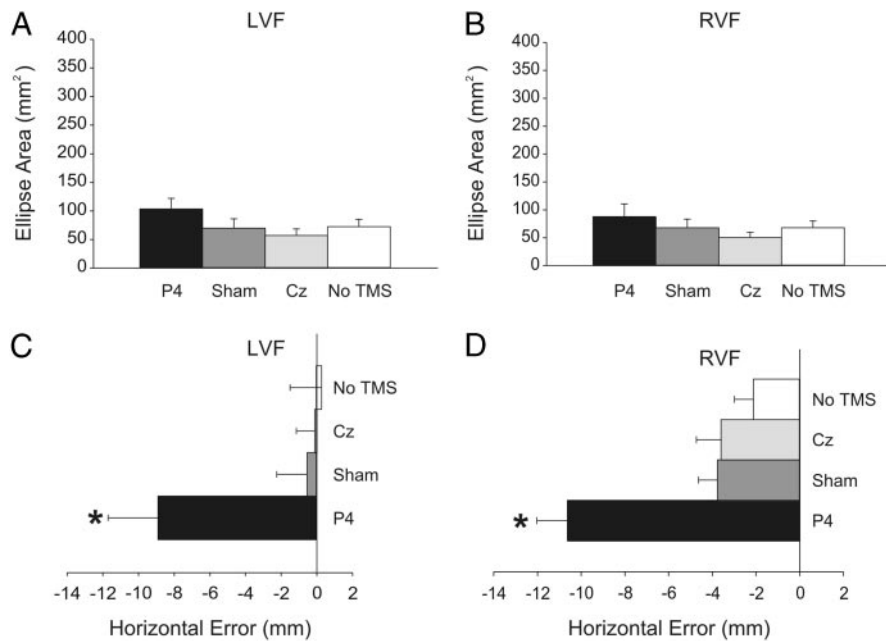


FIG. 4. Mean elliptical areas and horizontal error with dominant right hand in all 4 conditions for right hemispheric TMS with no prism. Figure follows the conventions of Fig. 3.

(LVF = P4: -8.88 ± 2.76 mm; baseline: 0.29 ± 1.74 mm; sham: -0.51 ± 1.68 mm; Cz: -0.11 ± 1.01 mm; and RVF = P4: -10.61 ± 1.38 mm; baseline: -2.11 ± 0.85 mm; sham: -3.74 ± 0.84 mm; Cz: -3.48 ± 1.11 mm). A direct comparison between the control conditions on both testing days (Session 1: Right TMS vs. Session 2: Left TMS) revealed significant differences in horizontal errors ($P < 0.05$) but not in elliptical areas ($P > 0.05$). The fact that there was an apparent inconsistency in the horizontal component of pointing in the control conditions between sessions may be the result of a practice effect or exposure to stimulation for the first time.

To distinguish whether TMS affected the speed-accuracy relationship, and verify that subjects did not use alternative strategies in stimulated conditions, we compared the mean movement times between stimulated and nonstimulated conditions for each session. For trials with TMS, movement times were similar (Session 1 = P4: 802.75 ± 56.54 ms; sham: 804.33 ± 56.50 ms; Cz: 809.67 ± 41.17 ms; and Session 2 = P3: 815.83 ± 78.18 ms; sham: 777.67 ± 59.28 ms; Cz: 779.25 ± 39.29 ms) compared with the nonstimulated conditions (Session 1 = baseline: 799.25 ± 58.92 ms; Session 2 = baseline: 807.17 ± 58.44 ms). Analyses revealed no significant influence of TMS on movement times ($P > 0.05$).

Experiment 1B: TMS during memory-guided pointing with left hand

We then repeated *Experiment 1A* with the nondominant left hand to investigate whether the same pattern persisted and, if so, whether it was spatially fixed or reversed with left-hand movement. It has been suggested that left/right PPC is preferentially responsible for control of the contralateral hand (Mendendorp et al. 2005; Perenin and Vighetto 1988). If TMS of the parietal cortex influenced the spatial memory representation of the target location, a similar pattern of endpoint movement should persist regardless of the effector used. Conversely, if this pattern reversed in spatial coordinates, it would suggest that parietal control of pointing was lateralized relative to the effector hand.

LEFT PARIETAL TMS. Figure 5, A–D and Fig. 6 use the same conventions as Fig. 2, A–D and Fig. 3, respectively, to show our findings during left PPC TMS with nondominant left-hand movement. Similar to the dominant right-hand movement results in *Experiment 1A*, Fig. 5, A–D shows that there was no systematic leftward or rightward shift in the horizontal reaching component coupled with a greater endpoint variability (elliptical area) in the left PPC stimulation condition (black ellipses) compared with the baseline condition (gray ellipses).

Again, we quantified these qualitative observations and analyzed the corresponding elliptical areas and horizontal reaching component from the overall movement performance. Figure 6 illustrates the main finding for the left PPC with the nondominant left-hand movement. As revealed by two separate two-way repeated-measures ANOVAs, condition (two levels: baseline and parietal stimulation) \times visual field (two levels: LVF and RVF) with respect to elliptical areas and mean horizontal reaching error, there was a significant main effect only for condition [$F_{(1,5)} = 12.29$; $P = 0.017$] in elliptical areas. Furthermore, post hoc analysis (Tukey) showed that stimulation over P3 significantly increased ($P = 0.01$) the elliptical area of pointing (LVF = 191.51 ± 96.98 mm²; RVF = 211.71 ± 96.84 mm²) compared with that of the nonstimulation baseline condition (LVF = 28.01 ± 13.88 mm²; RVF = 37.81 ± 15.32 mm²). This pattern of responses was consistent with the dominant right-hand movement results in *Experiment 1A*.

RIGHT PARIETAL TMS. Figure 5, E–H (right) and Fig. 7 both use the same conventions to show our findings but during right PPC TMS with nondominant left-hand movement. In this case, however, there was no significant increase in the scatter of the pointing endpoints during stimulation over P4 (black ellipses), but rather a systematic shift in ellipse centers (horizontal component error) to the left for all targets in both visual fields compared with the baseline (gray ellipses). Figure 7, consistent with the findings from Fig. 4 in *Experiment 1A*, quantitatively confirms that the elliptical areas were not significantly different

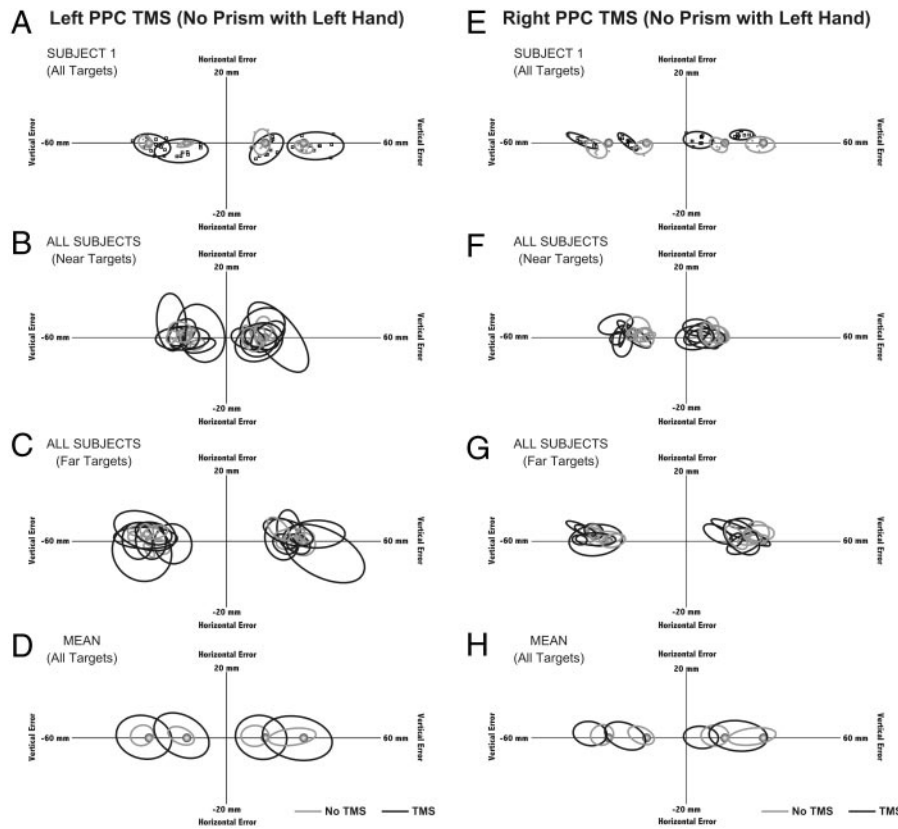


FIG. 5. Mean endpoint confidence ellipses with nondominant left hand during the delayed-pointing task for left (*left*) and right (*right*) hemispheric TMS with no prism. Figure follows the conventions of Fig. 2.

across the conditions and visual fields ($P > 0.05$). In addition, there was a significant main effect for condition [$F_{(1,5)} = 462.25$; $P < 0.001$] for the mean horizontal error during right parietal stimulation (LVF = -6.17 ± 2.03 mm; RVF = -10.26 ± 2.35 mm) compared with that in the baseline condition (LVF = -0.68 ± 1.42 mm; RVF = -4.79 ± 2.39 mm). Consistent with *Experiment 1A*, the directionality of the horizontal component of the pointing movement, but to a lesser degree, was systematically shifted leftward compared with the baseline independent of visual field.

To summarize the results of *Experiment 1*, we found that left parietal stimulation resulted in a significant increase in global pointing variability, but did not have significant differences in mean horizontal pointing error for both visual fields compared with those in baseline and control conditions. In contrast, right parietal stimulation did not affect endpoint variability, but systematically biased the mean horizontal error leftward for targets in both LVF and RVF. Furthermore, a similar pattern persisted, and remained spatially fixed, with the nondominant left-hand movement.

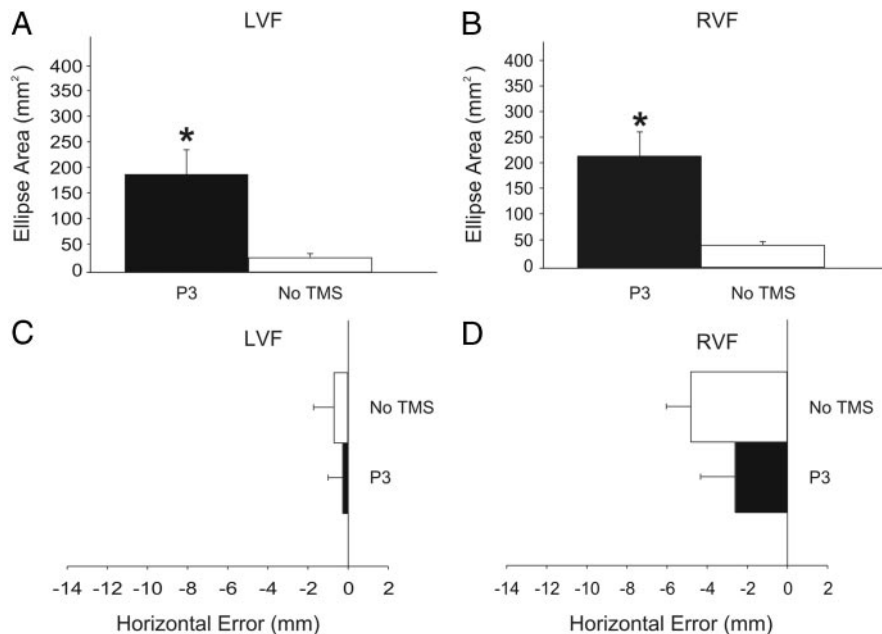


FIG. 6. Mean elliptical areas and horizontal error with nondominant left hand in the parietal and no stimulation conditions for left hemispheric TMS with no prism. Figure follows the conventions of Fig. 3.

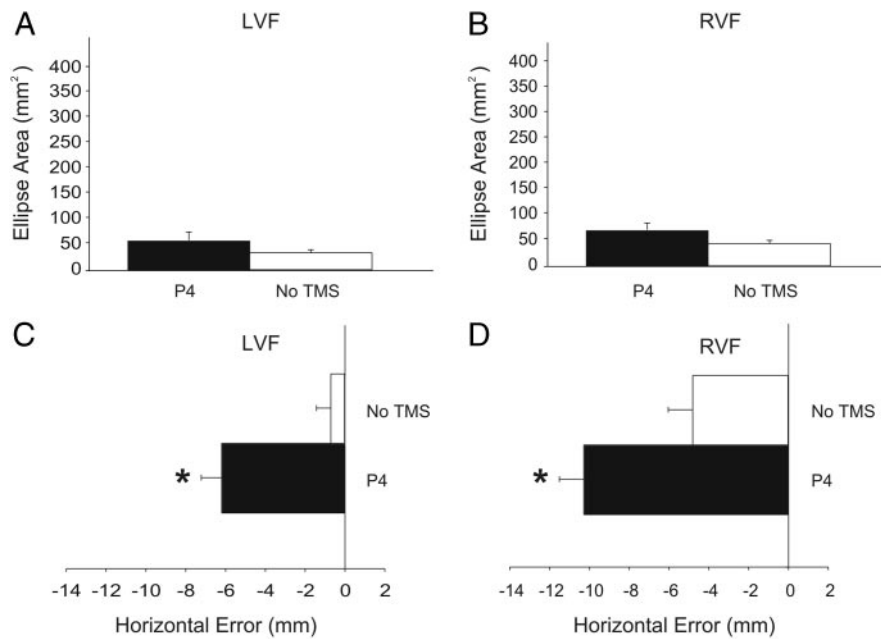


FIG. 7. Mean elliptical areas and horizontal error with nondominant left hand in the parietal and no stimulation conditions for right hemispheric TMS with no prism. Figure follows the conventions of Fig. 3.

Experiment 2: right PPC stimulation after prism adaptation

Given our result for right PPC, the critical question here is: Does this directional leftward bias in pointing error remain fixed in motor or visual coordinates? We addressed this question by using a left–right reversing prism adaptation paradigm in which the retinal coordinates of a target were dissociated from the corresponding motor command. It was previously shown (Marotta et al. 2005) that this reversal, in conjunction with the simple motor paradigm used here, leads to a rapid visuomotor adaptation that does not produce a dramatic, global left–right reversal of all the normal spatial contingency rules between visual input and motor output (Kohler 1962; Sugita 1996).

In *Experiment 2*, we trained subjects to point with the prism (see METHODS). As illustrated by Fig. 8A, subjects adapted their baseline pointing behavior (no TMS with no prism) from *Experiment 1A* (thin gray ellipses) to the baseline condition (no TMS with prism) in *Experiment 2* (thick gray ellipses) after prism training ($P > 0.05$; t -test). Figure 8, B and C illustrates the predicted outcomes of right TMS data with prism, using the right PPC data set from *Experiment 1A* with no prism. If the leftward bias in mean horizontal pointing error during right PPC TMS remained fixed in motor coordinates, then the right PPC stimulation data with prism would look the same as the right parietal TMS in *Experiment 1A* (Fig. 8B). Conversely, if the errors were fixed in visual coordinates (Fig. 8C), reversing vision would reverse the errors left to right. As predicted in Fig. 8B, the actual leftward shift in mean horizontal pointing error during right TMS after prism adaptation (Fig. 8D) remained fixed with respect to the actual movement and reversed with respect to the proximal retinal stimulus.

To quantify these findings across subjects, we plotted in Fig. 9 the average difference in pointing direction of the left and right peripheral targets between the no stimulation condition and P4 stimulation condition after the reversing prism adaptation session in *Experiment 2* (with prism) as a function of the average difference before that adaptation session in *Experiment 1A* (with no prism) for each subject. According to the visual

coordinate model (Fig. 8C), these differences should have an opposite sign. Accordingly, data from both the left (○) and right (■) targets should be represented in the *bottom half* of Fig. 9 (gray zone). In contrast, in the motor coordinate model (Fig. 8B) these data should have the same sign and should be represented in the opposite white zone (Fig. 9, *top*). As Fig. 9 clearly shows, the data of all six subjects followed the predictions of the motor coordinate model ($P > 0.05$; t -test). Thus the shift in pointing direction induced by TMS over right dorsal PPC appears to be fixed in motor coordinates.

DISCUSSION

It has long been argued that the parietal cortex plays a critical role in spatial processing and visually guided action (Andersen et al. 1997; Colby and Goldberg 1999; Goodale and Milner 1992; Jeannerod et al. 1995). Although recent studies showed that TMS over parietal regions disrupted on-line correction during limb movements (Della-Maggiore et al. 2004; Desmurget et al. 1999; Glover et al. 2005; Tunik et al. 2005) and other aspects of limb movement control concerning their integration with eye movements (van Donkelaar and Adams 2005; van Donkelaar et al. 2000), only one study to our knowledge used TMS to investigate the functional role of the PPC for spatial representation during a memory-guided pointing movement (Smyrnis et al. 2003).

As in the latter study, we delivered the TMS pulse during the memory interval only after viewing the stimulus, well before the pointing movement, so it is unlikely that this affected the on-line guidance of the movement (Desmurget et al. 1999). Likewise, we did not replicate the findings of van Donkelaar and Adams (2005) that TMS over PPC can deviate reach toward gaze, likely because the subjects were required to point immediately when the peripheral target appeared and the TMS was delivered at a more posterior parietal site.

The purpose of our first experiment was to investigate the functional relevance of the left and right dorsal PPC for spatial representation using a single-pulse TMS protocol during a memory-guided pointing movement. To summarize our main

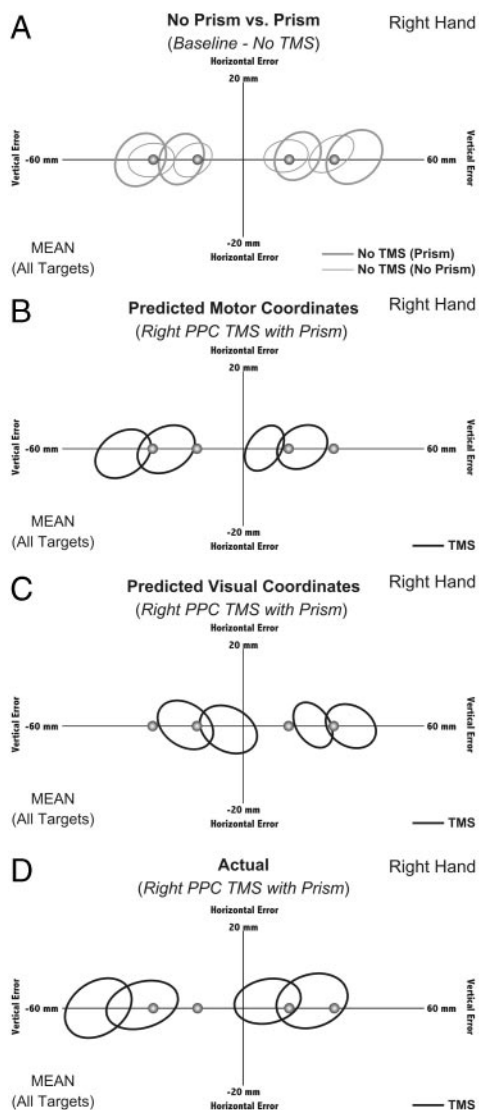


FIG. 8. Predicted vs. actual mean endpoint confidence ellipses for all subjects during right PPC TMS. *A*: mean endpoint confidence ellipses for all subjects during the delayed-pointing task for the baseline condition (no TMS with no prism) in *Experiment 1A* and the baseline condition (no TMS with prism) in *Experiment 2*. Figure follows the conventions of Fig. 2, *D* and *H*. Thin gray solid ellipses represent baseline with no prism, whereas thick gray ellipses represent baseline with prism. Subject quickly learned the prism task and showed a pattern of accurate and systematic pointing similar to original baseline errors with no prism. *B* and *C*: depiction of predicted outcome for mean horizontal pointing errors (black ellipses) in motor (*B*) and visual (*C*) coordinates using the data set from the no prism condition in *Experiment 1A* during right parietal stimulation (P4). *D*: illustration of elliptical fits of the actual mean horizontal pointing error after prism adaptation with prism during right parietal stimulation (black ellipses).

findings in *Experiment 1*: 1) there was a stochastically greater scatter of pointing endpoints in both visual fields during stimulation of left PPC, although no apparent systematic shift was observed in the pointing direction when compared with baseline and control conditions, and 2) in contrast, right PPC stimulation tended to systematically bias pointing leftward in the horizontal axis, independent of visual field, but did not significantly increase pointing scatter. The latter was not observed in the previous study by Smyrnis et al. (2003), presumably because they used a mouse-pointing task, whereas we

used an actual reach movement, or possibly because our figure-of-eight coil delivered a more focal pulse to the right PPC.

This finding confirms a causal role for left PPC in the generation of memory-guided reach movements (Smyrnis et al. 2003). In addition, our novel finding for right parietal stimulation agrees with the topography of right PPC (Medendorp et al. 2003) and may have been missed in previous TMS studies (Smyrnis et al. 2003) as the result of differences in methodology. In fact, such a pattern of hemispheric asymmetry was also observed in previous TMS studies that emphasized generally the importance of the right PPC in visuospatial and visual attentional tasks (Muri et al. 2002; Rushworth et al. 2001; Walsh et al. 1999), whereas left PPC played a dominant role in limb movements (Rushworth et al. 2001; Smyrnis et al. 2003).

Our finding that stimulation of left PPC results in misreaching with the right hand in both ipsi- and contralateral visual fields corroborates characteristic reaching disorders of patients with optic ataxia (Perenin and Vighetto 1988). Optic ataxia is a disorder associated with posterior parietal lobe lesions, in which visually guided reaching errors typically occur to peripheral targets (for reviews, see Battaglia-Mayer and Caminiti 2002; Rossetti et al. 2003). However, lesions confined to the right PPC in these patients typically result in misreaching with one or both hands only in the contralateral visual field (field effect) (Perenin and Vighetto 1988).

Recent reports described the rare phenomenon of magnetic misreaching, in which optic ataxia patients with parietal dam-

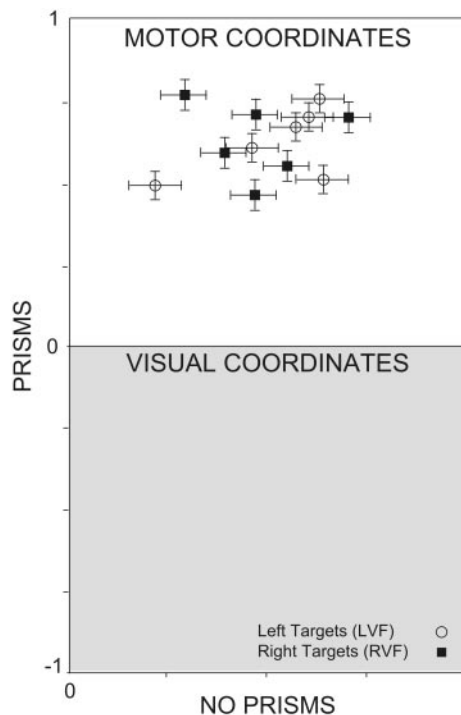


FIG. 9. Comparison of mean pointing error before and after prism adaptation. *x*-axis indicates the difference (\pm SE) in the mean pointing error between the no stimulation/baseline condition (No TMS) and right PPC stimulation (P4 TMS) before prism adaptation (with no prism) in *Experiment 1A*; *y*-axis is same but after prism adaptation (with prism) in *Experiment 2*. Encoding of visuospatial information in visual coordinates for memory-guided pointing requires movement endpoint data in the bottom panel (gray zone), whereas encoding in motor coordinates are represented with these data in the top panel (white zone) for both left- (\circ) and right-pointing targets (\blacksquare).

age are unable to decouple reach from gaze (Carey et al. 1997; Jackson et al. 2005). At first glance, our findings for right TMS over PPC might seem to contradict this patient work if one begins from the assumption that these low-intensity TMS pulses had an inhibitory effect in the parietal stimulation site. On the other hand, it is conceivable that right PPC stimulation orthodromically activated the dorsal PPC, transiently modulating elements of the neuronal network involved in our memory-guided pointing task. That is, this TMS-induced effect may have resulted in a globally leftward bias in our task. In fact, the leftward bias in pointing observed here during right PPC magnetic stimulation agrees with a recent report that showed an overall shift in reaching toward the left by an unilateral optic ataxia patient, suggesting an overall bias in pointing in the direction opposite to the lesion (Khan et al. 2006).

Taking our right PPC stimulation findings in *Experiment 1A* a step further, we probed whether this systematic leftward pointing shift remained fixed in visual or motor coordinates. In other words, is this transiently induced pointing error encoded upstream from the vision-to-motor transformation (Gottlieb and Goldberg 1999) or downstream from this transformation (Eskandar and Assad 1999; Kalaska 1996; Zhang and Barash 2000)? We tested this by dissociating the retinal coordinates of the goal from the corresponding motor command using an optical-reversing prism. Our results suggest that a brief TMS pulse modifies the output of the right PPC downstream from the adapted visuomotor reversal in motor coordinates, rather than modifying the visual coordinates of the memory representation.

A recent fMRI investigation (Fernandez-Ruiz et al. 2004) suggests that specific PPC regions encode neither vision nor movement per se, but rather something more intermediate and abstract, such as the spatial goal of the movement in retinal coordinates. Using fMRI, the authors used a delayed-pointing task to identify a cluster of PPC regions whose activity was topographically (contralaterally) related to the direction of the planned movement. All of these regions, including the putative human PRR (Connolly et al. 2003), showed a reversed topography when retested after training on an optical left-right reversing prism.

On its face, our result appears to contradict that of Fernandez-Ruiz et al. (2004). However, our stimulation site is inferior and lateral to the regions identified by these previous studies (Connolly et al. 2003; Fernandez-Ruiz et al. 2004; Medendorp et al. 2003, 2005; Prado et al. 2005) and, consequently, may represent different neural mechanisms. Moreover, the discrepancy between our fMRI and TMS results may underline the important differences between these techniques. In particular, fMRI correlates local field potentials with dendritic activity (i.e., input) (Logothetis et al. 2001) and correlates to physiology on a slow temporal scale. On the other hand, single-pulse TMS most probably acts on axons (i.e., output) (Pascual-Leone 2002) and may simulate a causal, short-term activation over a brief temporal duration.

Furthermore, it is noteworthy that various theoretical studies (Smith and Crawford 2005; Zipser and Andersen 1988) showed that a network implementing a reference frame transformation may encode sensory coordinates at the input correlative level and motor coordinates at the output causal level—even at the level of individual units. Therefore parietal cortex could encode both sensory coordinates and the prism transfor-

mation. Alternatively, it may be that the learned prism transformation works only on physiological patterns of input. In other words, TMS may bypass this transformation through “default,” unadapted pathways. In this scenario, the TMS shift would result from offsets in downstream motor structures such as dorsal premotor and motor cortex, which appear to use limb-centered frames of reference (Kakei et al. 1999; Kalaska and Crammond 1992; Sergio and Kalaska 2003).

Taken together, these data suggest that induction of a focal current reveals a hemispheric asymmetry in the early stages of the putative spatial processing in PPC. These results also suggest that a brief TMS pulse modifies the output of the right PPC in motor coordinates downstream from the adapted visuomotor reversal, rather than modifying the upstream visual coordinates of the memory representation.

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