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Transcranial Magnetic Stimulation Over Human Dorsal–Lateral Posterior Parietal Cortex Disrupts Integration of Hand Position Signals Into the Reach Plan

Michael Vesia,[1,2,5] Xiaogang Yan,[1,2] Denise Y. Henriques,[1,2,5] Lauren E. Sergio,[1,2,3,5] and J. D. Crawford[1,2,3,4,5]
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Vesia M, Yan X, Henriques DY, Sergio LE, Crawford JD. Transcranial magnetic stimulation over human dorsal–lateral posterior parietal cortex disrupts integration of hand position signals into the reach plan. *J Neurophysiol* 100: 2005–2014, 2008. First published August 6, 2008; doi:10.1152/jn.90519.2008. Posterior parietal cortex (PPC) has been implicated in the integration of visual and proprioceptive information for the planning of action. We previously reported that single-pulse transcranial magnetic stimulation (TMS) over dorsal–lateral PPC perturbs the early stages of spatial processing for memory-guided reaching. However, our data did not distinguish whether TMS disrupted the reach goal or the internal estimate of initial hand position needed to calculate the reach vector. To test between these hypotheses, we investigated reaching in six healthy humans during left and right parietal TMS while varying visual feedback of the movement. We reasoned that if TMS were disrupting the internal representation of hand position, visual feedback from the hand might still recalibrate this signal. We tested four viewing conditions: *1*) final vision of hand position; *2*) full vision of hand position; *3*) initial and final vision of hand position; and *4*) middle and final vision of hand position. During the final vision condition, left parietal stimulation significantly increased endpoint variability, whereas right parietal stimulation produced a significant leftward shift in both visual fields. However, these errors significantly decreased with visual feedback of the hand during both planning and control stages of the reach movement. These new findings demonstrate that *1*) visual feedback of hand position during the planning and early execution of the reach can recalibrate the perturbed signal and, importantly, and *2*) TMS over dorsal–lateral PPC does not disrupt the internal representation of the visual goal, but rather the reach vector, or more likely the sense of initial hand position that is used to calculate this vector.

INTRODUCTION

Goal-directed reaching involves transformations from visual inputs to motor commands for the arm (Andersen and Buneo 2002; Crawford et al. 2004). Converging evidence spanning primate neurophysiology (Batista et al. 1999; Battaglia-Mayer et al. 2000; Buneo et al. 2002; Galletti et al. 2003), human brain imaging (Astafiev et al. 2003; Beurze et al. 2007; Connolly et al. 2003; Medendorp et al. 2003, 2005; Prado et al. 2005), patient studies (Karnath and Perenin 2005; Perenin and Vighetto 1988), and transcranial magnetic stimulation (TMS) studies (Smyrnis et al. 2003; van Donkelaar and Adams 2005; van Donkelaar et al. 2000; Vesia et al. 2006) suggests that posterior parietal cortex (PPC) plays a critical role in these sensorimotor transformations.

Here, using TMS, we posed the specific question of whether human dorsal–lateral PPC is involved in incorporating initial hand position information into the reach plan. Presumably, a critical primary step in the planning of a goal-directed action is integrating information relating reach target and hand position. To reach for a visual object, the brain needs to specify the required reach movement vector by computing the difference between the internal estimate of current hand location and position of the object in space. These two estimates encode entirely independent information and are both equally necessary in the computation of the difference vector between target and hand position (Vindras et al. 2005). Therefore, it is not possible to rely on one more than the other. Target location is generally determined from visual information, but the sense of hand position can be localized in space through both vision and proprioception (Graziano et al. 2000; Rossetti et al. 1994, 1995). Topographic regions within PPC appear to play a crucial role in the integration of target and limb information for the planning of action in gaze-centered coordinates (Beurze et al. 2007; Buneo et al. 2002; Medendorp et al. 2005). Furthermore, patients with optic ataxia—a disorder ascribed to parietal lesions—exhibit impairments in the spatial integration of both visual and proprioceptive position information (Blangero et al. 2007, 2008; Khan et al. 2007).

We previously reported that single-pulse TMS over dorsal–lateral PPC perturbs the early stages of spatial processing for memory-guided reaching (Vesia et al. 2006)—that is, when vision of the hand was provided only at the end of the memory-guided movement, 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 reaching (contralateral to stimulation site) in both visual fields. In addition, the same lateralized pattern persisted with left-hand movement, suggesting that these aspects of parietal control of reaching movements are spatially fixed. Our data further suggested that TMS did not disrupt the visual coordinates of the memory representation, but rather the planned reach vector. However, our previous study did not show whether TMS disrupted either *1*) the reach vector directly, or one of the variables used to calculate this vector;

2) the reach goal in motor coordinates; or *3*) the sensory-derived internal estimate of the initial hand position.

To test between these hypotheses here, we investigated memory-guided reach accuracy and precision while varying visual feedback of the hand during TMS of the left and right dorsal–lateral PPC. We reasoned that if parietal TMS disrupts only the memory of reach goal—which did not vary between these paradigms—vision of the hand position in either the planning or control stage should not counteract the perturbing effect of TMS on reach performance. Alternatively, if parietal TMS were disrupting the internal sense of initial hand position, visual feedback from the hand might recalibrate this signal at the initiation, execution, or end of movement. We found that the systematic reaching errors and biases observed in our previous study significantly decreased when vision of the hand was provided during either the planning or the execution of the movement. This shows that TMS over dorsal–lateral PPC does not disrupt the internal estimate of the visual goal location, but rather the reach vector or, more likely, the sense of initial hand position that is used to calculate this vector.

METHODS

General

Six subjects, 22–32 yr of age, provided written informed consent to participate in the study. All participants were right-hand dominant, as defined by the Edinburgh Handedness Inventory (Oldfield 1971), with normal or corrected-to-normal visual acuity; in good-health; and, according to a self-report, without any known contraindications to TMS. All experiments received ethical approval by the York University Human Participants Review Subcommittee.

Localization of brain sites and TMS protocol

Single-pulse TMS was delivered at 60% of the stimulator output using a MagStim stimulator (MagStim, Whitland, UK) and a 70-mm figure-of-eight coil to the dorsal–lateral parietal cortex (Fig. 1*A*). The locus of TMS stimulation has a spatial resolution of approximately 0.5 to 1 cm (Brasil-Neto et al. 1992; Wilson et al. 1993) with an estimated penetration depth of roughly 2 cm (Epstein et al. 1990; Rudiak and Marg 1994), reflecting stimulation of the underlying cortex near the gray–white junction (Epstein et al. 1990). To localize left and right parietal areas, the TMS coil was placed over P3 and P4, respectively, according to the 10–20 EEG (electroencephalogram) coordinate system of electrode placement (Herwig et al. 2003; Okamoto et al. 2004), using commercially available 10–20 EEG stretch caps for 20 channels (Electro-Cap International, Eaton, OH). Specifically, test sites (P3 and P4) overlay left and right dorsal–lateral PPC, respectively, and included Brodmann area 19, adjacent cortex in the superior and inferior parietal lobule, a site that is situated over a part of the angular gyrus in the inferior parietal lobule and close to a posterior part of the adjoining intraparietal sulcus, and are consonant with cortical regions underlying these electrode positions reported elsewhere (Herwig et al. 2003; Koch et al. 2008; Okamoto et al. 2004; Vesia et al. 2006). Accordingly, these parietal stimulation sites could correspond to a region slightly more lateral to the putative human parietal eye fields (cf. Ryan et al. 2006), a region (or regions) thought to be homologous to macaque LIP, identified in previous human brain imaging (for review, see Culham and Valyear 2006; for examples, see Astafiev et al. 2003; Medendorp et al. 2003; Schluppeck et al. 2005; Sereno et al. 2001). Two additional control experiments were conducted to yield estimates of nonspecific effects of TMS. 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 for both left and right PPC. Last, we included a baseline "No TMS" condition where subjects received no stimulation while performing the task. The order of stimulation sites (left PPC, right PPC, vertex), sham conditions ("sham" left PPC, "sham" right PPC), and baseline control (No TMS) was counterbalanced across subjects in each experimental session.

All stimulation parameters were in accordance with the safety guidelines for magnetic stimulation (Wassermann 1998). Earplugs were provided to dampen the noise associated with the discharge from the TMS coil. None of the subjects reported any undesirable side effects as a result of the stimulation.
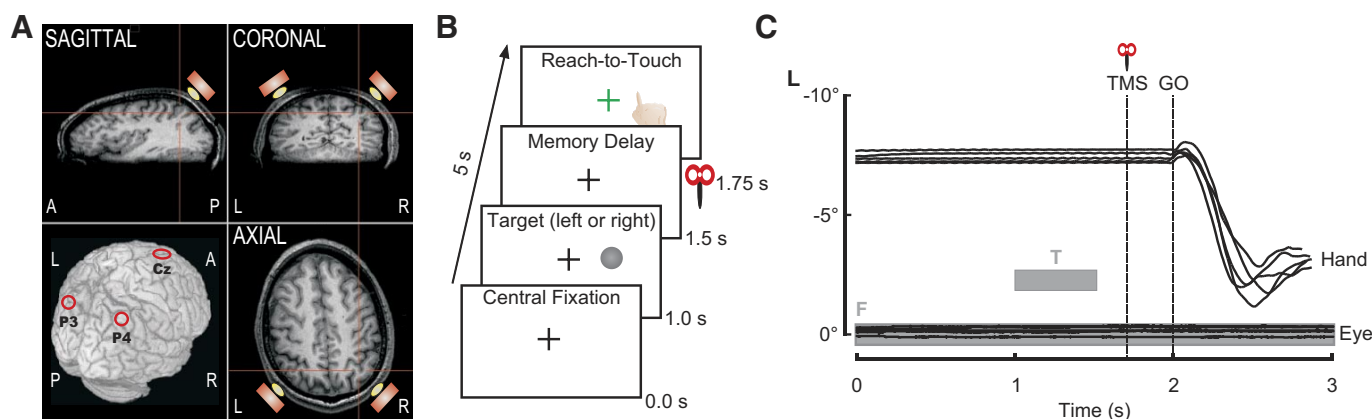

FIG. 1. Stimulation sites and experimental paradigm events. *A*: location of individual transcranial magnetic stimulation (TMS) sites for a typical subject are shown for dorsal–lateral posterior parietal cortex (PPC) with high-intensity signal markers placed on the subject's skull in the sagittal (*top left*), coronal (*top right*), and axial (*bottom right*) sections of T1-weighted magnetic resonance image (MRI). *Bottom left* shows a 3-dimensional rendering of the structural MRI. Red circles indicate the 3 cortical sites chosen for stimulation using the 10–20 electroencephalogram (EEG) coordinate system of electrode placement—test sites: left PPC (P3), right PPC (P4); and control site: vertex (Cz). *B*: delayed-reaching task. Subjects fixated a central cross for the duration of the trial. Then a peripheral dot (reach target) was presented to the left or right of fixation for 500 ms. A brief TMS pulse was delivered 250 ms after this peripheral target extinguished (on TMS trials only) during the memory-delay period. After the delay period, the central fixation cross changed color ("Go" signal) and signaled subjects to reach to the remembered peripheral target location. *C*: eye- and hand-position traces (solid black lines) along with experimental paradigm events during the reaching task plotted on a timescale. Thick gray boxes indicate the location and duration of the reach target (T) and fixation cross (F). Note that the eyes maintain central fixation when subjects reach to remembered target locations in either the TMS or No TMS conditions.

Experimental protocol

Our basic methodology was similar to that of our previous study (Vesia et al. 2006). Subjects sat in a dimly lit room with the head immobilized by a chin rest that aligned the dominant right eye with the central fixation cross. Subjects made open-loop reaches with their dominant right hand to peripheral targets displayed 30 cm away on a liquid crystal display screen in the frontal plane. Kinematic data were obtained by localizing the three-dimensional position of infrared light-emitting diodes taped to the index fingertip (sampling rate: 200 Hz; accuracy: ~0.2 mm; Optotrak 3020, Northern Digital, Waterloo, Ontario, Canada). Eye position was monitored using a head-mounted eye-tracking system (sampling rate: 360 Hz; Applied Science Laboratories, Bedford, MA).

Subjects performed the same basic task. At the start of each experimental trial, a central fixation cross appeared for 1,000 ms before a reaching target (0.5° circle) briefly appeared for 500 ms at one of four different locations in the periphery (16 mm left, 32 mm left, 16 mm right, 32 mm right relative to the central fixation cross). A single pulse of TMS was delivered 250 ms after this peripheral target extinguished (on TMS trials only) during the 500 ms memory-delay period. After the delay period, the central fixation cross changed color and signaled subjects to reach to the remembered peripheral target (Fig. 1B). Subjects maintained central fixation while reaching to the remembered peripheral targets in each stimulation condition (Fig. 1C).

Subjects performed two blocks of 12 trials to each of the four reach targets (two in the left and two in the right visual field) for all six stimulation conditions (No TMS, left PPC, "sham" left PPC, right PPC, "sham" right PPC, vertex) in each of the four viewing conditions (for a total of 2,304 trials; Fig. 2). We chose four different viewing tasks to distinguish visual control signals: 1) final vision of hand position (FIN) or late visual feedback epoch (Fig. 2A); 2) full vision of hand position (FUL) or planning and execution epochs (Fig. 2B); 3) initial and final vision conditions of hand position (INI) or planning epoch (Fig. 2C); and 4) middle and final vision conditions of hand position (MID) or early visual feedback epoch (Fig. 2D).

As shown in Fig. 2, we occluded the view of the subject's hand with an adjustable, opaque Lucite apparatus in the horizontal plane to
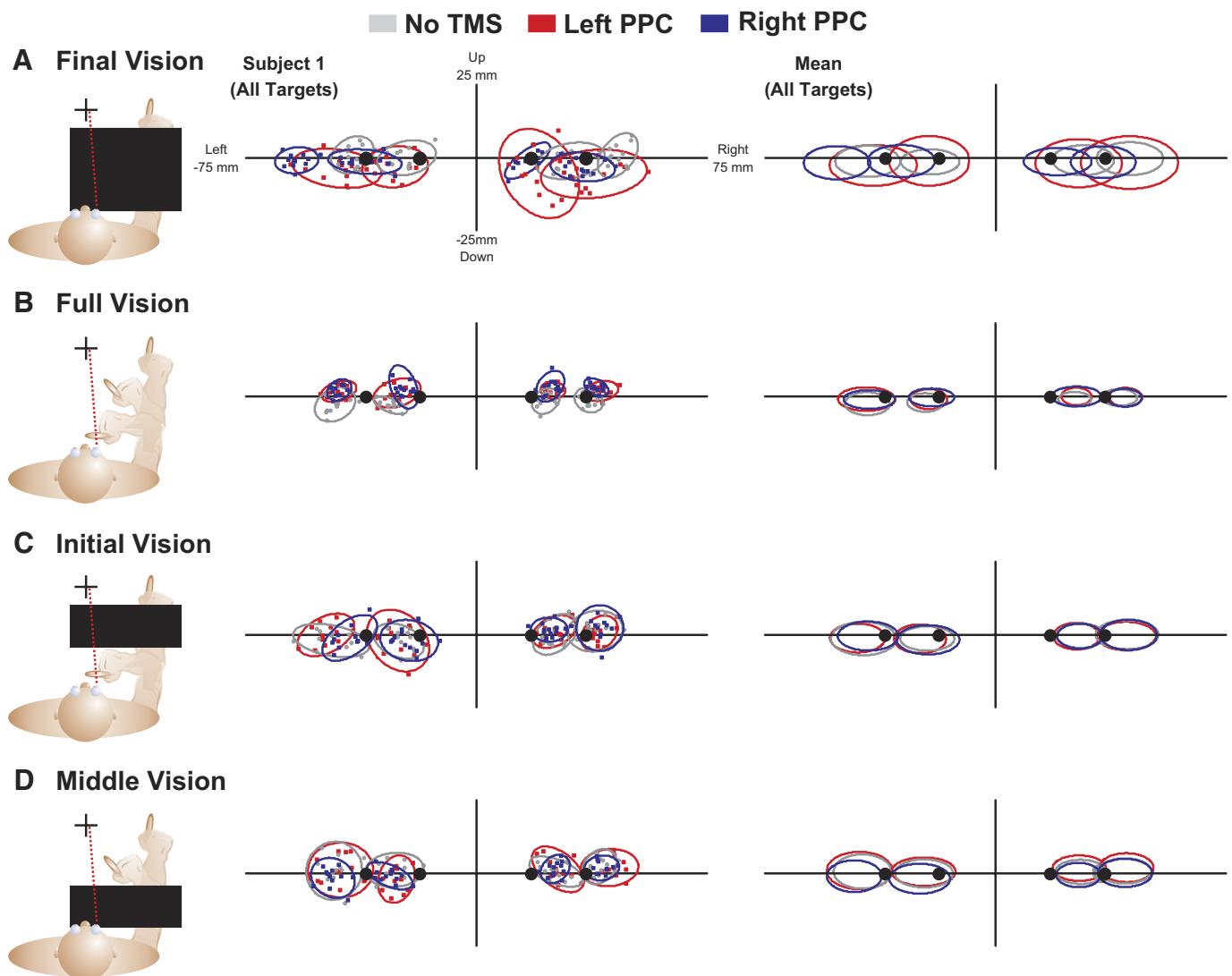

FIG. 2.   Individual subject and mean reach responses for all 6 subjects. *A–D* represent mean endpoint confidence ellipses for one typical subject (*left plots*) and mean elliptical fits for all 6 subjects (*right plots*) during the delayed reaching task in each of the 4 viewing tasks. Horizontal and vertical axes correspond to the *x*- and *y*-coordinates in the frontal plane while subjects fixated the central cross. Four possible reach targets (solid black circle) are shown in eye-centered coordinates from 32 mm left to 32 mm right of fixation. Individual reach endpoints are shown for control trials (No TMS; solid gray circle) and both left (solid red square) and right (solid blue square) parietal TMS as well as their mean elliptical fits in the no stimulation (gray ellipses), left (red ellipses), and right (blue ellipses) parietal stimulation conditions.

provide visual information of the hand only at these specified epochs. The length of the occlusion device varied for each viewing condition: 15 cm in INI; 10 cm in MID; and 25 cm in FIN. Since the distance between initial hand position and target position was held constant, the proportion of the occluded hand trajectory was constant independent of the subjects' arm length. In particular, this device allowed for subjects to view only their final hand position in FIN, static and final hand position in INI, hand position after movement onset in MID, and hand position throughout the entire planning and execution epochs in FUL. During INI and FUL conditions both the static hand position before movement onset and visual reaching target were viewed simultaneously in the periphery. These four viewing conditions were performed in a blocked design and all sessions were counterbalanced across subjects.

Our first viewing task (FIN; Fig. 2A) was similar to reaching in our previous experiment (Vesia et al. 2006) and served to replicate the TMS-induced reach deficits specifically produced by left and right parietal stimulation (baseline control in the current experiment). Our second viewing task (FUL; Fig. 2B) determined whether vision of the hand could negate the specific parietal TMS-induced reach errors after left and right parietal stimulation. Preliminary results showed that vision negated these parietal TMS-induced reach deficits so we added the latter two viewing tasks (INI and MID; Fig. 2, C and D, respectively) to tease apart when vision of the hand might counteract the perturbing effects of parietal stimulation. Note that both visual feedback of the hand at the end of the reach and proprioceptive information of the hand throughout the entire reach plan and execution were available for all four viewing tasks. Importantly, visual feedback information of the hand position varied for each viewing task, whereas visual information about the goal remained constant in all paradigms. That is, subjects never received visual feedback regarding reach errors relative to the goal so any differences between our paradigms were related to sensory calibration of hand position.

Data analysis

Performance was characterized by measuring the accuracy and precision of reach movement endpoints to visual targets in the horizontal (x) and vertical (y) axes in the frontal plane. In particular, reaching 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 two-dimensional (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 reaching scatter (Revol et al. 2003). The onset of reach movements was determined as the moment when velocity exceeded 5% of peak tangential velocity. Movement offset for reach was defined as the point at which the tangential velocity fell and remained below 5% of peak velocity. Movement time for the reach was thus obtained by subtracting the movement onset from the respective movement offset. The statistical reliability of differences between mean horizontal errors, elliptical areas, and mean movement times for reach were tested using repeated-measures ANOVA and Tukey post hoc tests.

RESULTS

As illustrated in Fig. 2, the paradigm consisted of four different tasks with regard to vision of the hand position relative to distinct planning and control stages of a memory-guided reach movement. Figure 2 (*left plots*) illustrates 2-D reach endpoints in the frontal plane for control trials (no stimulation; solid gray circle) and both left (solid red square) and right (solid blue square) PPC stimulation for one typical subject in the four viewing tasks. The fixation position was always straight-ahead (aligned with midsagittal plane of head), but the reach targets (solid black circle) varied from 32 mm left to 32 mm right of this fixation position. To quantify the systematic pattern of the reaching errors (i.e., accuracy) and depict the intraindividual variability (i.e., precision) of the reaching performance, we fitted 95% confidence ellipses to the movement endpoints for each of the four different reach targets for every subject in the four viewing tasks, and then averaged the parameters of these ellipses across subjects (Fig. 2, *right plots*; see METHODS).

Figure 2 shows mean reach response of an individual subject (*left plots*) and all six subjects (*right plots*) for the baseline No TMS trials (gray ellipses) and both left (red ellipses) and right (blue ellipses) PPC stimulation for each of the four viewing tasks. In baseline No TMS trials (gray ellipses), subjects reached too far peripherally relative to the central fixation point (Bock 1986; Henriques et al. 1998), but were otherwise fairly accurate. Consistent with our previous study (Vesia et al. 2006), parietal stimulation produced an increase in reach error and bias when vision of the hand was provided only at the end of the memory-guided movement (FIN; Fig. 2A). In particular, left PPC stimulation increased endpoint variability (red ellipses; Fig. 2A), whereas right PPC stimulation produced a systematic leftward directional shift in horizontal reaching, independent of visual field (blue ellipses; Fig. 2A), compared with baseline No TMS trials (gray ellipses; Fig. 2A). As clearly shown in Fig. 2B, we observed an improvement of reach accuracy and precision for both left and right PPC stimulation when vision of the hand position was provided throughout the task—in both the planning and control stages (FUL)—compared with the baseline FIN condition (Fig. 2A). As shown in Fig. 2C, after a brief simultaneous presentation of the static hand position before movement onset and target position during the planning stage (INI), endpoint variability and systematic leftward horizontal bias in reach endpoints decreased for left and right parietal stimulation, respectively. The same is true for reach responses when vision of hand position was provided immediately after movement onset during the early visual feedback stage (MID; Fig. 2D), suggesting that the inaccurate estimate of initial hand position can be visually updated at any stage in the planning and early execution of the reach movement. In some cases, TMS-induced errors were corrected during the hand trajectory in the MID condition, whereas these errors appeared to be negated from the start during the INI and FUL conditions (see Supplemental Fig. S1).[1]

To quantify these observations, we calculated the corresponding reach accuracy (horizontal reach error) and reach precision (elliptical area) for each stimulation and viewing condition in both left (LVF) and right (RVF) visual fields as

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[1] The online version of this article contains supplemental data.

shown in Fig. 3. These reach performance parameters were analyzed by two separate two-way repeated-measures ANOVAs for each visual field with factors viewing task (four levels: final, full, initial, or middle) and stimulation condition (six levels: No TMS, left PPC, "sham" left PPC, right PPC, "sham" right PPC, or vertex).

Figure 3, *A* and *B* illustrates the systematic horizontal error for all stimulation conditions for each of the four viewing tasks in the LVF (Fig. 3*A*) and RVF (Fig. 3*B*). Consistent with our previous study (Vesia et al. 2006), we found that there was a significant main effect for stimulation for the mean horizontal error in both LVF [$F_{(5,25)} = 2.51$; $P < 0.05$] and RVF [$F_{(5,25)} = 4.49$; $P < 0.01$]. However, viewing task was not significant [LVF: $F_{(3,15)} = 0.99$; $P = 0.42$; RVF: $F_{(3,15)} = 1.55$; $P = 0.24$]. Significance was also found for the interaction between the factors view and stimulation [LVF: $F_{(15,75)} = 6.38$; $P < 0.01$; RVF: $F_{(15,75)} = 21.49$; $P < 0.01$]. Post hoc analyses (Tukey) showed that right PPC stimulation with vision only at the end of the reach (FIN; solid red square) significantly biased the mean horizontal error compared with all other experimental

conditions for targets in both LVF and RVF ($P < 0.01$ in all comparisons; Fig. 3, *A* and *B*). Specifically, the directionality of the mean horizontal accuracy (merging data for all reach targets in the left and right visual fields) for right PPC stimulation in FIN relative to baseline No TMS for its respective viewing task (group mean response $\pm$ SE: FIN = -8.76 ± 2.54 mm, solid red square) was systematically shifted leftward compared with the other viewing tasks (FUL: 0.77 ± 0.74 mm, solid blue diamond; INI: 0.39 ± 0.43 mm, solid green triangle; MID: -2.51 ± 0.99 mm, solid black circle).

To verify that our results were not confounded by target position (i.e., reach targets of different retinal eccentricities), we compared reach endpoint accuracy of all four reach targets for all stimulation conditions relative to baseline No TMS in all viewing tasks. Consonant with our previous findings (Vesia et al. 2006), we confirmed that target position did not influence reach performance [$F_{(3,20)} = 0.59$; $P = 0.63$].

We repeated the same analyses for elliptical area as shown in Fig. 3*C* for the LVF and Fig. 3*D* for the RVF. As is clearly shown, irrespective of visual field, there was a significant main
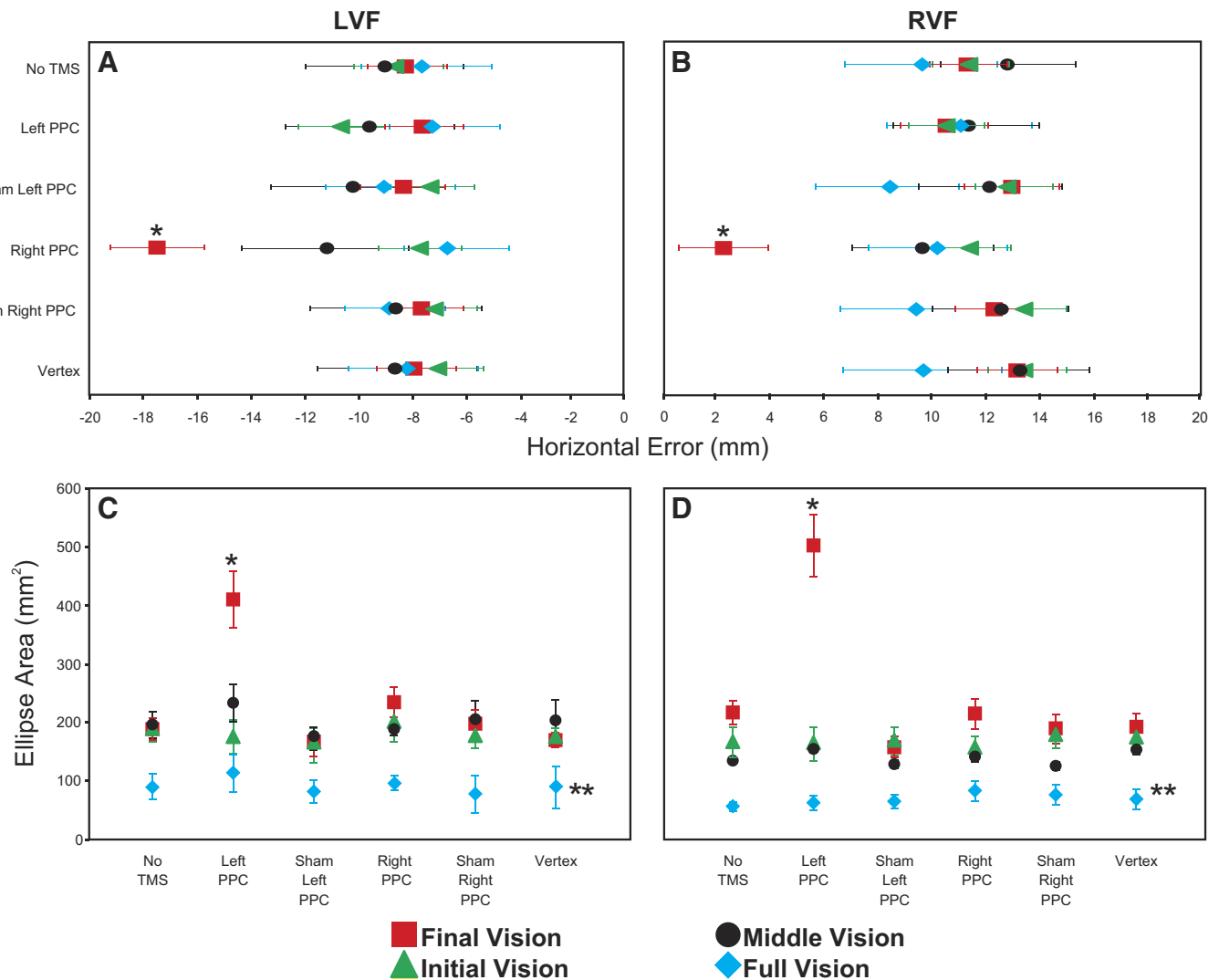

FIG. 3. Mean horizontal error and elliptical area in all 6 stimulation conditions. *A* and *B*: mean horizontal error for left visual field (LVF, *A*) and right visual field (RVF, *B*) reach targets for all 6 subjects and 4 viewing tasks: final vision (solid red sqaure); full vision (solid blue diamond); initial vision (solid green triangle); middle vision (solid black circle). *C* and *D*: mean elliptical area for LVF (*C*) and RVF (*D*). Asterisks indicate values showing significant differences ($P < 0.01$) using Tukey post hoc tests. Bars represent SE.

effect for view [LVF: $F_{(3,15)} = 33.24$; $P < 0.01$; RVF: $F_{(3,15)} = 38.61$; $P < 0.01$] and stimulation [LVF: $F_{(5,25)} = 6.31$; $P < 0.01$; RVF: $F_{(5,25)} = 11.88$; $P < 0.01$], as well as an interaction between these factors [LVF: $F_{(15,75)} = 2.75$; $P < 0.01$; RVF: $F_{(15,75)} = 9.71$; $P < 0.01$]. Post hoc analyses showed that there was significantly greater reach endpoint variability for left PPC stimulation in FIN (solid red square) compared with all other experimental conditions ($P < 0.01$, in all comparisons; Fig. 3, C and D). In particular, when we compared left parietal stimulation for each of the four viewing tasks (merging data for all reach targets in the left and right visual fields), endpoint variability (ellipse area) was about 67% larger on average in FIN (455.89 ± 109.76 mm^2; solid red square) compared with the other viewing tasks (FUL: 87.63 ± 25.58 mm^2, solid blue diamond; INI: 169.49 ± 74.95 mm^2, solid green triangle; MID: 193.99 ± 52.99 mm^2, solid black circle). In fact, endpoint variability robustly decreased nearly threefold with concomitant vision of the target position and hand position (INI) compared with FIN during left parietal stimulation. In addition, we also observed a comparable, significant influence on endpoint variability when vision was provided throughout the reach plan and movement (FUL vs. FIN; FUL vs. INI; FUL vs. MID; $P < 0.01$ in all viewing task comparisons; Fig. 3, C and D). Again, no differences were found between the four reach target positions [$F_{(3,20)} = 2.08$; $P = 0.13$].

Last, we conducted the same analysis on mean movement times of reach movements. We found that there was a significant main effect for stimulation [LVF: $F_{(5,25)} = 7.26$; $P < 0.01$; RVF: $F_{(5,25)} = 4.35$; $P < 0.01$], as well as an interaction between the view and stimulation factors [LVF: $F_{(15,75)} = 6.41$; $P < 0.01$; RVF: $F_{(15,75)} = 8.67$; $P < 0.01$]. However, the main effect for viewing task was not significant [LVF: $F_{(3,15)} = 0.24$; $P = 0.86$; RVF: $F_{(3,15)} = 1.35$; $P = 0.29$]. In particular, post hoc analyses revealed that only parietal stimulation conditions in the MID condition showed a statistically significant increase in movement time compared with all other experimental conditions ($P < 0.01$; Table 1). This is consistent with the idea that the MID viewing task allowed for on-line correction. Likewise, these movement times were not significantly different across all four reach targets in both visual fields [$F_{(3,20)} = 0.15$; $P = 0.93$].

DISCUSSION

The present study corroborates and extends our previous TMS findings that demonstrate the critical role of dorsal–lateral PPC in memory-guided reaching (Vesia et al. 2006). Here, by varying visual feedback of hand position and maintaining sensory information of the reach target location constant, we demonstrate for the first time that TMS over the

dorsal–lateral PPC directly disrupts the reach vector or, more likely, the internal sense of initial hand position that is required to calculate this vector, rather than the internal representation of the reach goal. Critically, these systematic reaching errors and biases significantly decrease when vision of the hand was provided during either the planning or execution stages of the reach movement. Given that this visual information was irrelevant to the goal of the movement, and that presentation of the goal did not vary, performance could improve only if this visual information was used to update an internal estimate of initial hand position, which could be disrupted by parietal TMS. This suggests that 1) dorsal–lateral PPC possesses an estimate of initial hand position in the early stages of the reach plan; 2) this estimate is used in the calculation of the reach vector (i.e., reach vector = goal position − hand position); and 3) that this estimate can be visually updated at any stage in the planning and early execution of the reach.

These findings are consistent with the notion that the parietal cortex is involved in the early computation of the extrinsic reach vector command (Buneo et al. 2002; Desmurget et al. 1999). It is likely that the reach goal information required to compute this vector is represented elsewhere, for example, in the more medial–posterior region of the parietal cortex, often called the "human parietal reach region" (Connolly et al. 2003; Culham and Valyear 2006; Culham et al. 2006; Fernandez-Ruiz et al. 2007). Based on this, we predict that TMS of the parietal reach region would produce the opposite effect: disruptions of the reach vector as a function of the goal, not the sense of initial hand position.

Our findings show that TMS over the dorsal–lateral PPC disrupts the reach vector command in our FIN vision paradigm, perhaps by perturbing the initial hand position input required to calculate this vector. We also should consider a second possibility—that TMS directly perturbs the reach vector after information of hand position is subtracted from goal position. Regions of PPC this far posterior are not generally thought to encode reach kinematics independent of the goal and hand positions (Buneo and Andersen 2006; Fernandez-Ruiz et al. 2007; Medendorp et al. 2008). Nonetheless, we will consider several theoretical frameworks that assume the reach vector was directly perturbed.

First, if the reach vector is initially calculated, then perturbed directly by TMS, and then *not* updated, vision of the hand could not influence reach performance. This contradicts our FUL, INI, and MID vision parietal stimulation data. Second, the vector could be calculated, then perturbed directly by TMS, but then updated continuously over the time course of the movement. However, even if vision dominates proprioception when both are present, proprioception is still used when vision is not available (Andersen et al. 1997; Desmurget et al. 1995;

TABLE 1. *Summary of movement times in the four viewing tasks for all stimulation conditions*

	No TMS	Left PPC	"Sham" Left PPC	Right PPC	"Sham" Right PPC	Vertex
Final vision	669.89 (41.61)	659.85 (37.38)	691.84 (50.04)	690.85 (51.58)	675.73 (49.44)	683.45 (44.81)
Full vision	645.58 (46.31)	640.16 (45.64)	665.51 (56.32)	674.48 (54.71)	650.58 (54.15)	657.71 (51.14)
Initial vision	671.57 (70.44)	657.42 (72.82)	675.27 (83.28)	661.98 (67.51)	660.41 (56.99)	676.48 (68.69)
Middle vision	687.67 (19.77)	800.76 (32.48)*	687.57 (18.03)	819.01 (25.97)*	686.74 (13.17)	662.66 (18.05)

*Values are means and SEs are shown in parentheses for merged data for all 6 subjects for all 4 targets in both visual fields. All movement times are in milliseconds. Statistical analyses indicated a significant difference in movement times for left and right PPC stimulation in the middle vision task compared to all other stimulation conditions and viewing tasks. Asterisks indicate values showing significant differences, $P < 0.01$, using Tukey post hoc tests.

Graziano et al. 2000; Rossetti et al. 1995; Wise et al. 1997). Therefore this model contradicts our FIN task, where the TMS-induced errors occurred despite the presence of constant proprioceptive feedback. Third, a hybrid combination of the latter two frameworks is possible. Suppose that *1*) the system can use either vision or proprioception to calculate the reach vector; *2*) TMS then perturbs the reach vector; but then *3*) only vision of hand position (but not proprioception) can be used to update this vector. In this scenario, proprioception would not be able to correct the TMS-induced errors in the FIN condition, but vision would be able to correct the errors in the other conditions (which is what we found). We prefer the simple explanation that parietal TMS disrupts the sense of hand position and this erroneous signal is overridden by vision of the hand. However, these two possibilities are so closely interrelated that they cannot be disentangled in the present experiment. Further, both agree that it was not the goal, but rather something correlated to hand position, that was disrupted in our experiment.

How, then, is this hand position information integrated with goal information to calculate the reach vector? One possible explanation may be that parietal cortex selectively mediates the integration of initial hand position information into the reach plan on the basis of both visual and proprioceptive signals. This scheme is consistent with evidence that PPC orchestrates these visual, somatosensory, and motor signals in the early planning stages of a reach (Andersen et al. 1997; Batista et al. 1999; Battaglia-Mayer et al. 2000; Caminiti et al. 1999; Snyder et al. 1997). The present experiment, however, cannot address whether the hand position signal that is disrupted is proprioceptive or visual in origin, or both. Given the multimodal nature of the cells in the cortical regions that we stimulated, it is likely that both these signals provide initial hand position information in everyday situations, where both vision and proprioception are available.

Our previous results (Vesia et al. 2006) showed that a similar pattern of TMS-induced reach deficits persists, remaining spatially fixed, with the nondominant left-hand movement. These findings suggested that our dorsal–lateral PPC stimulation site is responsible for the spatial representation of the end-effector position independent of the hand used. However, other studies have suggested that left PPC and right PPC are preferentially responsible for control of the contralateral hand (Chang et al. 2008; Medendorp et al. 2005; Perenin and Vighetto 1988; Rice et al. 2007). The differences between these studies could be due either to the precise localization of stimulation or to the modulation of neural activity in remote and interconnected cortical regions within the network (Paus 2002).

Primate neurophysiology has identified a region in the medial aspect of the PPC—often called the "parietal reach region" (PRR)—that encodes the transport aspect of reach (Batista et al. 1999; Calton et al. 2002; Snyder et al. 1997). Human PPC contains a region (or regions), perhaps analogous to monkey PRR—located more medially relative to the parietal stimulation sites used in the current study (Astafiev et al. 2003; Beurze et al. 2007; Connolly et al. 2003; DeSouza et al. 2000; Medendorp et al. 2003, 2005; Prado et al. 2005)—that selectively encodes the visual reach goal (Fernandez-Ruiz et al. 2007). Converging evidence spanning primate neurophysiology (Battaglia-Mayer et al. 2001; Buneo et al. 2002) and human neuropsychology (Beurze et al. 2007; Blangero et al.

2007, 2008; Khan et al. 2007; Medendorp et al. 2005; Perenin and Vighetto 1988) suggests that PRR and surrounding regions, which are linked by reciprocal association connections, are modulated by hand position in a manner that potentially could be used to encode the reach vector. Perhaps the region of parietal cortex targeted in our study may be disrupting a primary site that directly inputs to these areas. Alternatively, we cannot rule out that stimulation of dorsal–lateral PPC could potentially propagate to more distant sites indirectly via interconnected areas across the neuronal circuit that are involved in reach planning. Our knowledge concerning the TMS mechanisms of action, however, is still limited to drawing absolute conclusions (Pascual-Leone et al. 2000; Robertson et al. 2003).

Primate neurophysiology further suggests that parietal cortical areas encode target location in gaze-centered coordinates (Batista et al. 1999; Colby and Goldberg 1999; Snyder et al. 1997). It recently has been shown that hand proprioceptive information—even in the absence of vision—is also transformed into a gaze-centered coordinate system (Blangero et al. 2005; Buneo et al. 2002). This has led to the proposal that hand–target comparisons occur in gaze-centered coordinates at the level of PPC (Andersen and Buneo 2002; Batista et al. 1999; Blohm and Crawford 2007; Buneo and Andersen 2006; Medendorp et al. 2005). Alternatively, hand and target positions could be compared in body-centered coordinates (Carrozzo et al. 1999; Flanders et al. 1992; Henriques et al. 1998; McIntyre et al. 1997, 1998) or in both gaze- and body-centered coordinates (Battaglia-Mayer et al. 2001, 2003; Khan et al. 2007). Any of these schemes is consistent with our current data.

Our findings are also consistent with the results from both optic ataxic and neglect patients (Husain et al. 2000; Jakobson et al. 1991; Mattingley et al. 1998; Milner et al. 2003; Roy et al. 2004) and previous TMS studies (Koch et al. 2008; Smyrnis et al. 2003; Vesia et al. 2006) that suggest the parietal cortex is involved in the planning of reach movements. In contrast, several other patient studies (Blangero et al. 2008; Grea et al. 2002; Pisella et al. 2000; Schindler et al. 2004) and TMS studies (Desmurget et al. 1999; Glover et al. 2005; Rice et al. 2006; Tunik et al. 2005) have suggested that PPC also plays a critical role in the on-line control of reaching and grasping, but not in the planning phase of the movement (Rice et al. 2006).

The difference between these interpretations could arise from either methodological or anatomical differences. For instance, in Rice et al. (2006), dual-pulse TMS was delivered during the viewing period of stimulus presentation, whereas in our study single-pulse stimulation was delivered during the memory-delay period after stimulus presentation. Also, these discrepancies may be due to the different conditions used—such as reaching or grasping with unconstrained gaze in previous TMS studies—versus reaching to peripheral visual targets with central fixation in our current experiment. Here, subjects used peripheral vision to view both the target and the visual feedback of the hand during the reach, which is unusual in a more natural context. We tested subjects in this manner to account for possible visual field effects, which did not turn out to influence the TMS-induced errors. Although optimal accuracy is achieved when hand and eye movements are combined—and subjects normally reach to a target after foveal capture—there may be situations where foveal capture is indeed not possible, or is not optimal, such as when reaching for

a cup of coffee while continuing to read the newspaper. Besides, empirical evidence suggests that peripheral vision or memory (or both) is often used in naturalistic settings, without degrading hand movement accuracy (Johansson et al. 2001). Therefore our task is natural in a least some contexts. However, foveation might be a more important factor for studies of brain areas that encode the goal, as opposed to the hand position network that we perturbed here.

Moreover, the site of stimulation in our current study mainly targeted the inferior parietal lobule in a region of the posterior aspect of the intraparietal sulcus, whereas in previous studies TMS was applied to more anterior parietal regions at the junction between the anterior aspect of the intraparietal sulcus and the inferior postcentral sulcus. Given the distinct cortical systems for central and peripheral vision (Clavagnier et al. 2007; Karnath and Perenin 2005; Prado et al. 2005), and numerous functional subregions within parietal cortex (Culham and Kanwisher 2001; Culham and Valyear 2006; Culham et al. 2006), these differences may be crucial.

Finally, our finding that early visual feedback recalibrates misperceptions of hand position confirms existing psychophysical experiments that show the importance of visual information about the position of the hand before movement onset for action planning (Desmurget et al. 1995, 1997; Elliott and Madalena 1987; Prablanc et al. 1979; Rossetti et al. 1994, 1995; Vindras et al. 1998). Recent imaging findings also have implicated the human PPC in the maintenance of a coherent body image when the brain receives conflicting multisensory information—i.e., sensory discrepancy between limb movement positions sensed by vision and proprioception (Clower et al. 1996; Inoue et al. 1997, 2000). Further, a detailed case study suggests that the parietal cortex is critical for sensorimotor integration and maintenance of an internal estimate of limb position (Wolpert et al. 1998). This supports the existence of a mechanism that combines visual and proprioceptive signals to provide the most accurate estimate of initial hand position (Desmurget and Grafton 2000).

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