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Original Article

ORIGINAL ARTICLE

Transcranial Magnetic Stimulation Over the Human Medial Posterior Parietal Cortex Disrupts Depth Encoding During Reach Planning

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Abstract

Accumulating evidence supports the view that the medial part of the posterior parietal cortex (mPPC) is involved in the planning of reaching, but while plenty of studies investigated reaching performed toward different directions, only a few studied different depths. Here, we investigated the causal role of mPPC (putatively, human area V6A–hV6A) in encoding depth and direction of reaching. Specifically, we applied single-pulse transcranial magnetic stimulation (TMS) over the left hV6A at different time points while 15 participants were planning immediate, visually guided reaching by using different eye-hand configurations. We found that TMS delivered over hV6A 200 ms after the Go signal affected the encoding of the depth of reaching by decreasing the accuracy of movements toward targets located farther with respect to the gazed position, but only when they were also far from the body. The effectiveness of both retinotopic (farther with respect to the gaze) and spatial position (far from the body) is in agreement with the presence in the monkey V6A of neurons employing either retinotopic, spatial, or mixed reference frames during reach plan. This work provides the first causal evidence of the critical role of hV6A in the planning of visually guided reaching movements in depth.

Key words: human V6A, transcranial magnetic stimulation, reaching in-depth, reach plan, eye-hand configuration

In humans and monkeys, the medial posterior parietal cortex (PPC) has a major role in monitoring and guiding reaching movements (Goodale and Milner 1992; Jeannerod et al. 1995; Andersen et al. 1997; Colby and Goldberg 1999; Culham et al. 2006; Cavina-Pratesi, Monaco et al. 2010; Filimon 2010; Fattori et al. 2017). Studies on patients revealed that PPC lesions lead to a neurological condition called optic ataxia, which results in incorrect reaching movements toward targets located in peripheral vision, whereas reaching toward foveated targets are correctly performed (Perenin and Vighetto 1983; Perenin and Vighetto 1988; Karnath and Perenin 2005; Rossetti et al. 2005; Blangero et al. 2009; Vallar and Branch Coslett 2018).

In the monkey, the medial part of the PPC hosts area V6A (Galletti et al. 1999; Gamberini et al. 2011), whose neurons are modulated by reaching movements toward foveated as well as peripheral targets (Bosco et al. 2015; Fattori et al. 2001, 2005, 2017; Marzocchi et al. 2008; Bosco et al. 2016). Recent electrophysiological works highlighted the modulating effect of both

direction and depth (i.e., amplitude) of reaching movements on V6A neurons (Hadjidimitrakis, Bertozzi, Breveglieri, Bosco et al. 2014). A lesion study on macaque monkeys showed that, when V6A was surgically removed, the animals showed misgrasping and hypometric misreaching (Battaglini et al. 2002), particularly evident when reaching was directed toward targets located far from the animal (Galletti et al. 2003).

In humans, the cortical lesion of optic ataxia patients is centered in the medial parieto-occipital cortex (Karnath and Perenin 2005), a region which likely involves the human homologous of macaque area V6A (hV6A) (Pitzalis et al. 2013, 2015; Tosoni et al. 2015). Some patients with lesions in the PPC show more significant visuomotor deficits in-depth than in direction, which lead to a specific impairment of arm movements toward targets arranged at different distances from their body (Holmes and Horrax 1919; Baylis and Baylis 2001; Danckert et al. 2009). However, as human studies typically involve large lesions, it is difficult to correlate a specific deficit with a single cortical area and, conversely, no human patient with a lesion restricted to the hV6A has been studied to date.

Transcranial magnetic stimulation (TMS) represents a unique opportunity to fill this gap of knowledge because it allows to reversibly perturb restricted, selected brain regions on the cortical surface and to test their causal role on behavior (Pascual-Leone et al. 1999). The TMS studies involving the medial PPC (mPPC) conducted so far (Ciavarro et al. 2013; Dessing et al. 2013; Vesia et al. 2010, 2013, 2017) demonstrated a specific involvement of the mPPC in encoding peripheral reaching. Specifically, Vesia et al. (2010) and Ciavarro et al. (2013) showed that a train of repetitive TMS applied over the mPPC during reach planning caused a deviation of memorized reaching endpoint toward the position of visual fixation (misreaching) that resembled optic ataxia deficits. However, the repetitive TMS paradigm prevented the possibility to investigate the timing of the mPPC involvement. Even more importantly, as participants in these prior studies only performed peripheral reaching and reaches to targets located at different depths were not tested, it remains speculative whether the human mPPC plays causal roles in guiding the arm toward foveated targets and specifically at different depths.

Thus, to address these questions, we investigated the causal role of human mPPC (putatively hV6A according to Ciavarro et al. 2013; Pitzalis et al. 2013; Tosoni et al. 2015) in the encoding of depth and direction of reaching movements in different eye-hand configurations (foveal and peripheral reaching). To this aim, we used single-pulse TMS (spTMS) administered at two time-points during the reaction time (planning phase before the movement onset) of an immediate, visually guided reaching task.

Materials and Methods

Participants

Fifteen healthy volunteers (3 males and 12 females; age range 20–29 years; mean age 22.6 ± 2.49 years) participated in this study. The number of participants has been determined basing on a power analysis, that indicated that a sample size of 15 participants is necessary to achieve a statistical power (1-β) of 0.90 (two-tailed $\alpha = 0.05$; effect size $f = 0.20$; number of measurements = 18; correlation = 0.6, analysis performed with G*Power software (Faul et al. 2007).

All the participants were right-handed according to a standard handedness inventory (Briggs and Nebes, 1975), had normal or corrected-to-normal visual acuity in both eyes, and were naïve as to the purposes of the experiment. None of the participants had neurological, psychiatric, or other medical problems or any contraindication to TMS (Rossi et al. 2009). Participants provided written informed consent, and the procedures were approved by the Bioethical Committee at the University of Bologna (Prot. 170133, 21 November 2018) and were in accordance with the ethical standards of the 2013 Declaration of Helsinki. No discomfort or adverse effects during TMS were reported or noticed.

Localization of Brain Sites

To identify the target area hV6A, we used frameless stereotaxic neuronavigation. Before each experimental session, the coil position was identified on each participant's scalp wearing a bathing cap using the SofTaxic Navigator system (EMS, Bologna, Italy) (Carducci and Brusco 2012; Valchev et al. 2017; Avenanti et al. 2018). In a first step, skull landmarks (nasion, inion, and two preauricular points) and 65 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra Optical Tracking System (Northern Digital, Inc., Waterloo, ON, Canada). Coordinates in Talairach space were automatically estimated by the SofTaxic Navigator from an magnetic resonance imaging (MRI)-constructed stereotaxic template. This procedure has been proven to ensure a good localization accuracy, showing an error of roughly 5 mm in comparison to methods based on individual MRIs (Carducci and Brusco 2012).

The Talairach coordinates we used were $x = -10$, $y = -78$, $z = 40$ (Fig. 1A) (Talairach and Tournoux 1988). These coordinates are the same as used in a previous TMS study on hV6A (Ciavarro et al. 2013), and are similar to those used for studying the Superior parieto-occipital cortex (SPOC) (Vesia et al. 2010, 2013, 2017), a region also investigated in imaging studies (Cavina-Pratesi, Monaco et al. 2010; Gallivan et al. 2009, 2011; Rossit et al. 2013; Monaco et al. 2014) that likely includes hV6A (Fattori et al. 2017). In each participant, the hV6A scalp sites were marked on the bathing cap with a pen. Then, the neuronavigation system was used to estimate the projections of the scalp sites on the brain surface. Mean coordinates ± standard deviation corresponded to the hV6A (mean $x = -10.2 \pm 1.3$, $y = -76.9 \pm 2.9$, $z = 40.6 \pm 2.5$).

TMS was also applied to the occipital cortex (area V1/V2) to control for the nonspecific effects of the TMS stimulation (Kamitani and Shimojo 1999; Chiappini et al. 2018). To target V1/V2, the coil was centered 2 cm dorsal to the inion (Romei et al. 2016), holding the handle tangentially to the scalp and pointing downward.

TMS Protocol

Biphasic spTMS was delivered using a MagStim Rapid2 stimulator and a 70 mm figure-of-eight coil. Stimulation of hV6A was carried out by placing the coil tangentially over the marked scalp sites along a parasagittal line with the handle pointing downward (Vesia et al. 2010).

Sham stimulation was performed by placing the coil tilted at 90° over the vertex, so that no current was induced in the brain (Lisanby et al. 2001). As known from previous experiments (Lisanby et al. 2001; Sandrini et al. 2011), by adopting this procedure, no effective magnetic stimulation reached the brain

during the sham condition, while the participants' feeling of coil-scalp contact and discharge noise were similar to the real stimulation. We administered sham stimulation over a single site (the vertex) instead of over each of the target areas to provide a single control condition for both hV6A and occipital sites, that is, avoiding an increase in the number of trials (Lockwood et al. 2013; Jacquet and Avenanti 2015; Amemiya et al. 2017; Paracampo et al. 2018).

To minimize potential TMS aftereffects on cortical activity that outlast the period of direct stimulation (Pascual-leone et al. 1994; Wang et al. 1996; Levkovitz et al. 1999; Siebner and Rothwell 2003; Siebner et al. 2009) while keeping the duration of the experiment acceptable, the intertrial period of the task (see below) was randomly set at 5–7 s. Custom software externally triggered the TMS at reaching target onset, as explained below (see Behavioral task).

The intensity of magnetic stimulation was fixed at 70% of the maximal stimulator output as in Smyrnis et al. (2003) and similar to several previous TMS studies targeting the PPC (Lewald et al. 2002; Dambeck et al. 2006; Vesia et al. 2006; Buelte et al. 2008; Prime et al. 2008; Vesia et al. 2010; Delle Monache et al. 2017).

None of the participants reported the presence of scotoma in the visual field during and immediately after TMS, nor any undesirable side effects as a result of the stimulation.

Apparatus and Behavioral Task

We tested the influence of TMS of the hV6A on reaching preparation by using the apparatus used in a recent psychophysical study (Bosco et al. 2017). It consisted of a 19-inch touchscreen (ELO IntelliTouch 1939 L) laid horizontally on a desk located at waist level. It contained the targets of reaching movements performed by the participants with their right hand. In all trials, participants started the reaching movement with their hand on a button (home-button) placed adjacent to the touchscreen in front of the participant's chest, as sketched in Figure 1B. The participants performed immediate (i.e., without delay) reaching movements.

The reaching movements were performed in a darkened room. The head of participants was supported by a chin rest in order to reduce head movements. The stimuli were green (fixation point, diameter 0.3 cm) and red (reaching target, diameter 1.2 cm) dots presented at different depths and in different directions with respect to participant's midline (Fig. 1B). The stimuli had a luminance of about 17 cd/m^2. The visible display size of the touchscreen was 37.5×30 cm. It contained 15.500 touchpoints/cm^2. The display had a resolution of 1152×864 pixels and a frame rate of 60 Hz.

Figure 1B shows target positions with respect to the participant's body. There were nine possible locations where targets could appear: three placed at a near distance (18.5 cm from the initial hand position), three at an intermediate distance (30 cm from the initial hand position), and three at a far distance (41.5 cm from the initial hand position, Fig. 1B). The targets were arranged in a square of 23×23 cm, and were located 11.5 cm apart from each other, either on the left or the right side; the central targets were placed along the sagittal midline. All targets were located within a comfortable reaching distance for all participants tested.

The task presented different eye/target configurations (see Fig. 1C): the "constant gaze configuration", in which the eye fixated a central fixation target and the hand reached to one of the eight peripheral reaching targets; the "constant reach configuration", in which the eyes fixated one of the eight peripheral targets and the hand always reached the central target; and "foveal reach configuration", in which fixation and reaching targets were coincident. Notice that in both constant gaze and constant reach configurations, the position of the fixation point was not coincident with the position of the reaching target, so they were all peripheral reaching.

The sequence of visually guided reaching (Fig. 1D) consisted of an intertrial period (intertrial) whose duration was randomly chosen between 5 s, 6 s, or 7 s, followed by the presentation of the fixation point that prompted the participant to press the home button. Then, the participant had to stare at the fixation point (fixation) for a period whose duration was randomly chosen trial by trial (1.3 s or 1.5 s). After this period, the reaching target appeared (Cue/Go) and this indicated: 1) the position to reach, 2) that the participant had to promptly reach that target position while maintaining fixation on the fixation target (immediate reaching).

To investigate the timing of the involvement of hV6A in action planning, we delivered a spTMS at two different timings (100 ms or 200 ms) from target onset (Go signal) in different trials. We selected these two times as they tap early versus later phases of reach planning while falling well within participants' reaction time (Supplementary Table S1). The fixation point and reaching target remained illuminated until the participant completed the arm movement (visually guided reaching). When the participant touched the target on the touchscreen (movement offset), the target and fixation point switched off and a new intertrial period started.

The task was composed of 30 blocks of 25 trials each (8 trials for constant gaze condition, 8 for constant reach condition, and 9 for foveal reach condition) for a total of 750 trials performed over the same experimental session. Each session lasted approximately 3.5 h. Fifteen blocks were composed of 100-ms trials, and 15 of 200-ms trials. Out of each 15 blocks of trials, five blocks involved active stimulation of hV6A, five active stimulation of V1/V2, and the remaining five sham stimulation. Within each block, trials of the three configurations were randomized. We also randomized blocks of 100-ms and 200-ms of each stimulation condition (hV6A, V1/V2, Sham). For stimuli presentation and data analysis, we used Matlab (Mathworks, USA) with the Psychophysics Toolbox extension (Brainard 1997).

Data Analysis and Acquisition

The kinematics of reaching movements was recorded using a motion tracking system (VICON motion capture system, 5 M cameras, 1024×1024 pixel resolution) by sampling the position of two markers at a frequency of 100 Hz; markers were attached to the wrist (on the scaphoid bone) and the nail of the right index finger (reaching finger). The trajectories of reaching movements of an exemplary participant in the Sham condition during different eye-hand configurations are shown in Supplementary Figure S1.

Reaching onset was detected by the release of the home button. Reaching offset was detected by the touch on the touchscreen. We defined the reaction time as the interval between the "Go" signal and movement onset. Movement time was obtained by subtracting the movement onset from the respective movement offset. Participants were asked to move the hand in a ballistic way (without pauses or interruptions), at a fast but comfortable speed, and as accurately as possible.

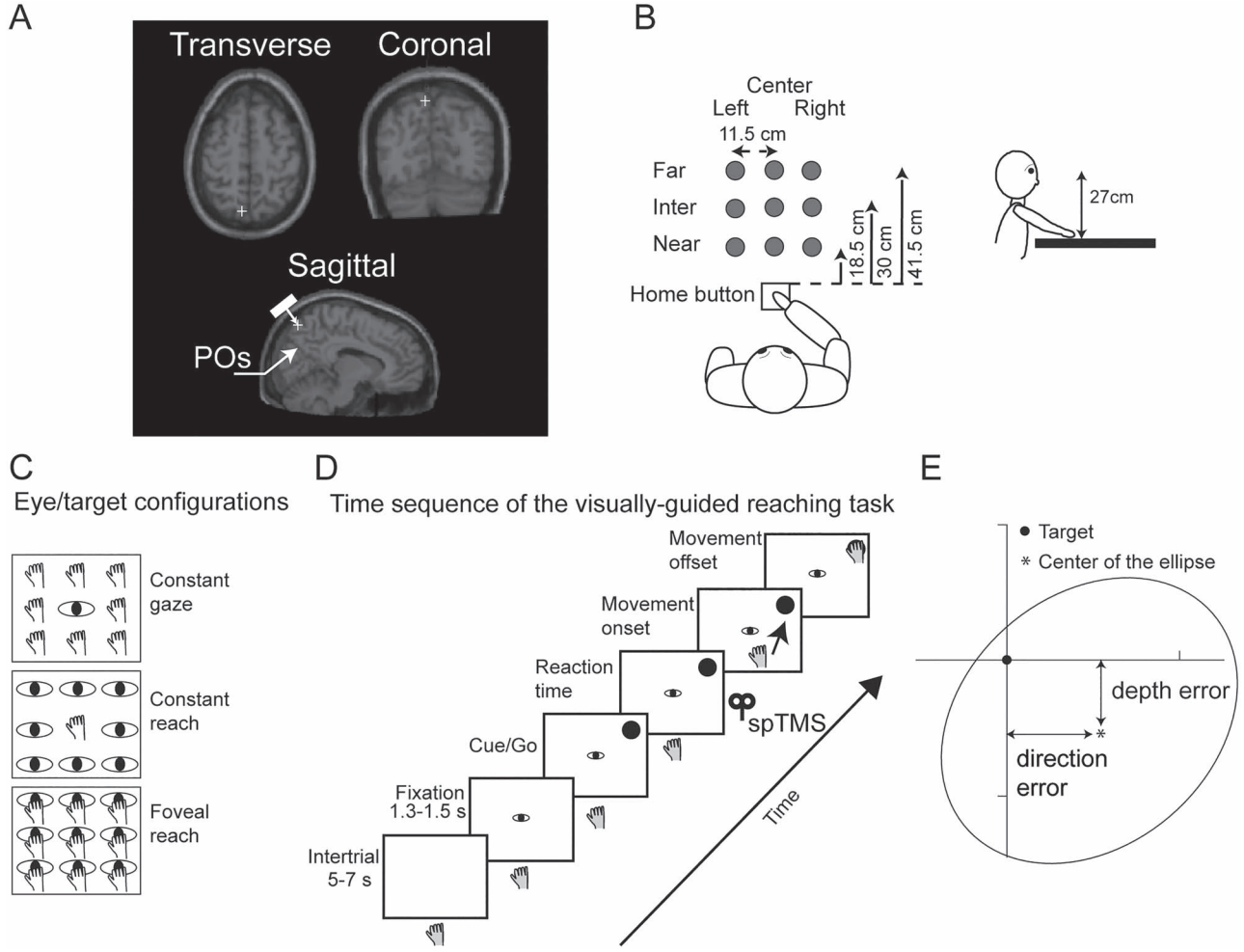

Figure 1. Experimental setup (*A*) targeted hV6A site (indicated with white crosses) displayed in a transverse (top left), sagittal (bottom), and coronal (top right) template brain section in one exemplary subject. (*B*) Top (left) and lateral (right) view of the target arrangement in the experimental task. The participants performed reaching movements with their right hand toward one of the nine targets (gray dots) located at different depths (far, intermediate, and near) and in different directions (left, center, and right). Reaching movements were performed in a darkened room from the initial hand position located next to the body (home button), indicated by a square. (*C*) Top view of the three task configurations. Top panel, constant gaze configuration: reaching movements were performed toward one of the nine targets (hands). The spatial position of the target changed trial to trial, but the gaze was kept constant at the central position. Central panel, constant reach configuration: reaching movements were always performed toward the target located in the central position. During the execution of the task, participants had to fixate one of the nine different positions (eyes). Bottom panel, foveal reach configuration: reaching movements were performed toward one of the nine targets. During the task, the participant fixated and reached the same target (eye and hand on the panel). (*D*) Time sequence of visually guided reaching (only constant gaze configuration is shown for conciseness). The small eye depicted in the figure represents the fixation point; the filled black dot represents the reaching target. The fixation point (a green point on the touchscreen) stayed on for 1.3 or 1.5 s and then the reaching target (a red point on the touchscreen) was turned on in one of the locations. Immediately, the participant had to reach with her/his right hand the visible position of the target while maintaining fixation on the fixation target (immediate reaching). During the reaction time, spTMS was delivered after 100 ms (100 ms-trial) or 200 ms (200 ms-trial). The fixation and the reaching targets were visible until the participant completed the movement. (*E*) Sketch of the measurements of the precision and the accuracy of the reaching movements. An exemplary 95% confidence ellipse is shown, as well as the indication of depth and direction errors. "Target" represents the reaching target.

Eye position was recorded using a camera-based eye-tracker (Pupil Lab, Pupil Labs Gmbh) recording real-time gaze position at 200 Hz. The elevation distance between the eyes of participants and the touchscreen was 27 cm (Fig. 1B). Before collecting data from each participant, the equipment was calibrated using a five-point grid that the participants were asked to fixate steadily.

Movement accuracy and precision were extracted by endpoints recorded by the touchscreen and derived from the parameters of 95% confidence ellipses fit to hand position (end-point) distributions measured at movement offset, as performed in previous studies (Vesia et al. 2006, 2008, 2010). Constant error (accuracy) was calculated by taking the signed difference between the horizontal (horizontal error, here referred to as direction error) and vertical (vertical error, here referred to as depth error) coordinates of the center of movement ellipses and each target location (Fig. 1E). Positive direction errors indicate reach end-points to the right of the target; positive depth errors indicate reach end-points nearer to the body than the target. Variable error (precision) was measured using the area of these ellipses (Fig. 1E). Statistical reliability of differences between mean constant errors, variable error, reaction, and movement times was tested using repeated-measures ANOVA and Duncan's post hoc tests. In particular, we performed separate three-way repeated-measures ANOVAs, for

each eye-target configuration and depth/direction dimensions with the following factors: Stimulation condition (three levels: Sham, V1/V2, hV6A), stimulation time (two levels: 100 ms, 200 ms), depth (three levels: near, intermediate, far) or direction (three levels: left space, center, and right space).

Analysis of gaze positions during the trials was performed (offline) in order to ensure that participants fixated the fixation point during both reaching execution and preparation. This control was particularly important for trials of the constant gaze and constant reach configurations, where the positions of the reaching target and fixation point were incongruent. Trials where gaze fixation was not directed to the fixation point, were excluded from the subsequent analysis (percentage of removed trials: ~4%). To do this, we have first checked offline the movies created by the pupil lab system to exclude trials where the gaze was directed far away from the fixation point. Then, we have also excluded the trials where the coordinates of the gaze positions recorded in the period between target onset and movement end were out of a window that contained the two standard deviations of these coordinates (Fisher et al. 2017).

Since our aim was to assess the critical role of the hV6A in planning reaching movements, in the main text we report only the main effect or interaction of the stimulation condition, while other effects have been described in the Supplementary material.

Results

Constant Gaze Configuration (Peripheral Reaching)

Reach end-point precision

Reach end-point precision is expressed by the area of 95% confidence ellipses of the scatter of the fingertips at movement end (Fig. 1E). Stimulation of hV6A (or V1/V2) did not appear to influence this measure (Supplementary Fig. S2A), in line with previous works targeting similar brain regions (Vesia et al. 2010; Marigold et al. 2019). Effects on precision of depth and direction are reported in the Supplementary material.

Reach end-point accuracy: direction error

The analysis of constant error pattern of reaching end-points revealed a weak main effect of stimulation condition ($F_{2,28} = 4.4$, $P = 0.02$, partial $\eta^2 = 0.24$; Fig. 2A and Supplementary Fig. S3A). This effect appeared driven by a rather small (<1 mm) but significant increase in direction errors following V1/V2 stimulation (mean values ± SE: 5.6 mm ± 0.34) relative to sham (4.9 mm ± 0.37; $P = 0.009$) and by a similar effect, although nonsignificant, following hV6A stimulation (5.39 mm ± 0.36; $P = 0.06$). The small increase in direction errors was comparable between the two active conditions ($P = 0.36$) and thus it possibly reflected unspecific effects of active TMS.

Direction error was strongly affected by reaching direction ($F_{2,28} = 14.99$, $P < 0.001$, partial $\eta^2 = 0.52$; Fig. 2B), and in all cases participants touched the screen to the right of the targets (see positive direction errors in Fig. 2B). The highest direction errors were observed during reaches to the left space (8.03 mm ± 0.71), intermediate to the central space (4.94 mm ± 0.26), lowest to the right (2.99 mm ± 0.78; all comparisons, $P < 0.04$). So, the highest direction errors were observed in the hemispace (left) opposite to the arm used (the right one), as one would expect when the arm moves to the opposite hemifield, given the extra cost to be paid by participants to redirect attention across the vertical meridian with respect to when they have to move attention within one visual quadrant (meridian-crossing effect) (Downing and Pinker 1985; Hughes and Zimba 1985, 1987; Rizzolatti et al. 1987; Tassinari et al. 1987; Gawryszewski et al. 1992; Reuter-Lorenz and Fendrich 1992).

Reach end-point accuracy: depth error

spTMS delivered over hV6A produced significant depth errors (Fig. 2D), in agreement with the strong influence of the depth of reaching movements in monkey V6A (Hadjidimitrakis, Bertozzi, Breveglieri, Bosco et al. 2014). Specifically, hV6A stimulation applied 200 ms after the Go signal, during the reaction time, affected depth error for reaches to the farthest targets (Fig. 2D and Supplementary Fig. S3B) as shown by the interaction effect of stimulation condition by stimulation time by depth ($F_{4,56} = 3.00$; $P = 0.03$, partial $\eta^2 = 0.17$). Post hoc analysis showed no influence of TMS in 100-ms trials across the different target positions (all $P > 0.12$; see Fig. 2C), but a clear influence of TMS for 200-ms trials, particularly for far target positions, where hV6A stimulation caused larger depth errors (5.29 mm ± 1.48) relative to sham (3.74 mm ± 1.68; $P = 0.03$) and V1/V2 stimulation (3.37 mm ± 1.26; $P = 0.01$), which in turn did not differ from one another ($P = 0.58$).

No significant influence of TMS was observed for intermediate (hV6A: 1.56 mm ± 1.07; V1/V2: 1.95 mm ± 1.01; Sham: 2.93 mm ± 0.83; all comparisons $P > 0.05$) and near target positions (hV6A: 3.83 mm ± 1.05; V1/V2: 3.60 mm ± 0.89; Sham: 4.64 mm ± 0.62; all comparisons $P > 0.15$).

In sum, V6A stimulation delivered 200 ms after the Go signal caused hypometric misreaches, in particular when targets were located farther than the gaze position. This suggests an inaccurate encoding of the depth of reaching targets. The increase in hypometric misreach of far targets caused by hV6A stimulation was not associated with changes in action timing as no significant change in reaction times or movement times were detected (reaction time: interaction stimulation condition by stimulation time by depth $F_{4,56} = 1.56$; $P = 0.20$; partial $\eta^2 = 0.10$; movement time: interaction stimulation condition by stimulation time by depth, $F_{4,56} = 1.99$; $P = 0.11$; partial $\eta^2 = 0.12$; see Supplementary Table S1 for mean values).

Constant Reach Configuration (Peripheral Reaching)

Reach end-point precision

Stimulation over hV6A did not influence the end-point precision in the constant reach configuration when considering direction (main effect of stimulation condition or interactions by stimulation condition, all $F < 2.9$, all $P > 0.07$, all partial $\eta^2 < 0.17$). When considering depth, a significant main effect of stimulation condition was found ($F_{2,28} = 4.1$, $P = 0.03$, partial $\eta^2 = 0.23$). Post hoc comparisons revealed that precision after hV6A stimulation did not differ from precision after Sham stimulation (Sham = 6.63 cm^2 ± 0.75; hV6A = 6.37 cm^2 ± 0.75; $P = 0.30$, see Supplementary Fig. S2B). Nevertheless, stimulation over V1/V2 led to an increase in precision of reaching compared to Sham (V1/V2 = 5.93 cm^2 ± 0.64, $P = 0.01$, Supplementary Fig. S2), but reaching precision was not different compared to hV6A ($P = 0.09$). Other effects on precision are described in the Supplementary material.

Reach end-point accuracy: direction error

We did not find any significant effects of TMS over hV6A on direction errors (main effect of stimulation condition or interaction by stimulation condition, all $F < 1.36$, all $P > 0.26$, all partial

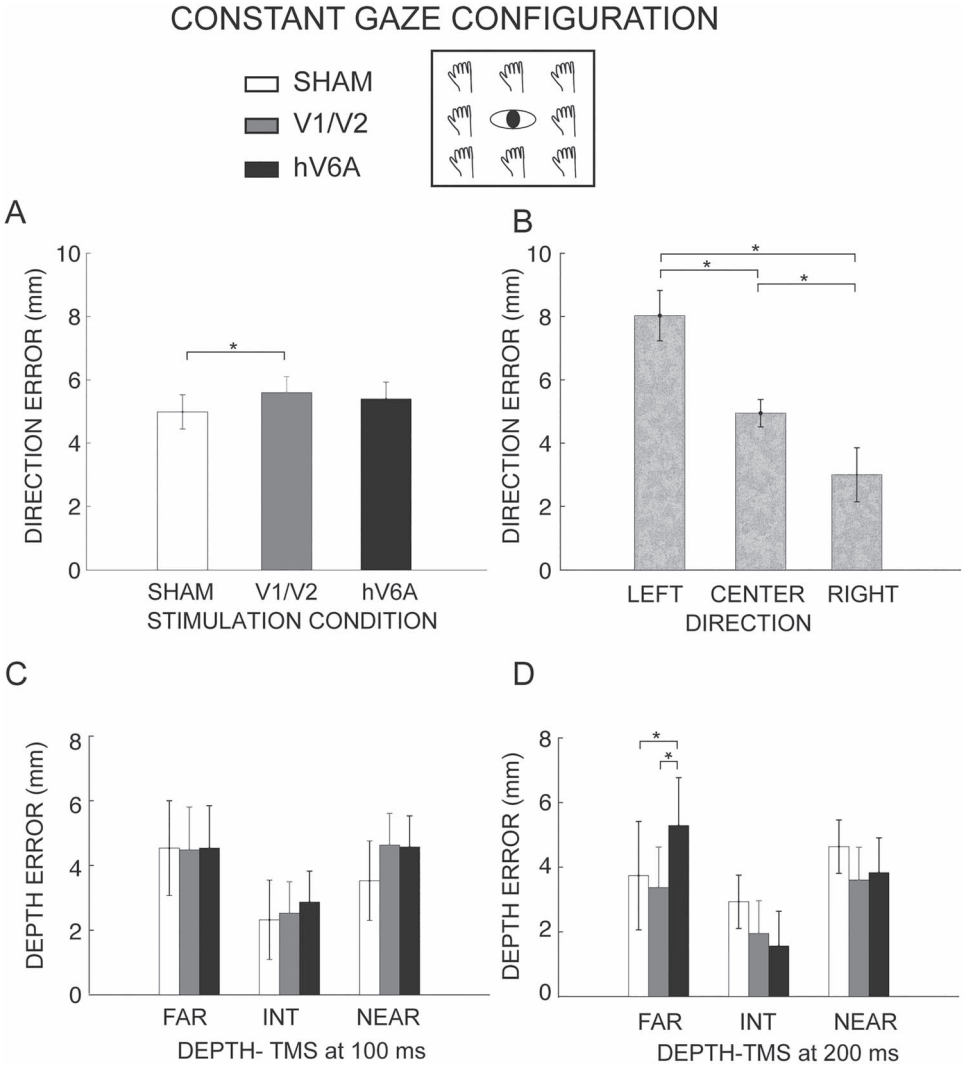

Figure 2. Accuracy in the constant gaze configuration. (*A*) Distribution of direction errors in TMS delivered during Sham stimulation (SHAM, white), V1/V2 stimulation (V1/V2, dark gray), and hV6A stimulation (hV6A, black). A main effect of the stimulation condition was evident, due to a decrease in accuracy after V1/V2 stimulation. (*B*) Distribution of direction errors in the different directions of reaching. LEFT = left targets, INT = intermediate targets, RIGHT = right targets. Accuracy was influenced by the direction of reaching. (*C*) Distribution of depth errors in the different stimulation conditions at different depths of reaching during 100-ms trials. No effect of TMS is shown. (*D*) Distribution of depth errors in the different stimulation conditions at different depths of reaching during 200-ms trials. After spTMS over hV6A after 200 ms from the Go signal, reaching movements toward far targets were performed less accurately. FAR = reaching targets far from the body, INT = intermediate reaching targets, NEAR = reaching target near to the body. Asterisks indicate significant post hoc comparisons ($P < 0.05$).

$\eta^2 < 0.08$). However, similarly to the constant gaze configuration, in the constant reach configuration, the reach end-point accuracy was deeply influenced by gaze direction ($F_{2,28} = 21.7$, $P < 0.001$, partial $\eta^2 = 0.61$, Fig. 3A), with gradually larger errors when the gaze was directed to the left of the reaching target, that is, in the opposite hemispace (5.8 mm ± 0.65) in comparison to the center (3.5 mm ± 0.37) and, in turn, to the right (2.48 mm ± 0.49; all comparisons $P < 0.04$).

Reach end-point accuracy: depth error

Despite the effect observed in depth in the peripheral reaching in the constant gaze configuration, hV6A stimulation did not affect depth errors in the constant reach configuration (main effect of stimulation condition or interactions by stimulation condition, all $F < 2.61$, all $P > 0.09$, all partial $\eta^2 < 0.16$). This demonstrates that the TMS effect directly acted on the accuracy of arm movement while the decoupling of gaze and hand positions per se was not enough to observe it: a change in the final position of arm movement is also required. Indeed, TMS was effective when the hand reached a position that was farther than the gaze in the constant gaze configuration, but it was not effective when the hand reached a position that was farther than the gaze in the constant reach configuration. This suggests that V6A encoding of the depth of reaching is not influenced uniquely by the relative position of hand and gaze (effectiveness of TMS in peripheral but not in foveal reaching), but also by the distance of the hand from the body. This is in agreement with the overwhelming presence in the monkey V6A of neurons with mixed retinotopic/spatial reference frames during reaching (Marzocchi et al. 2008; Hadjidimitrakis, Bertozzi, Breveglieri, Fattori et al. 2014; Bosco et al. 2016; Hadjidimitrakis et al. 2017).

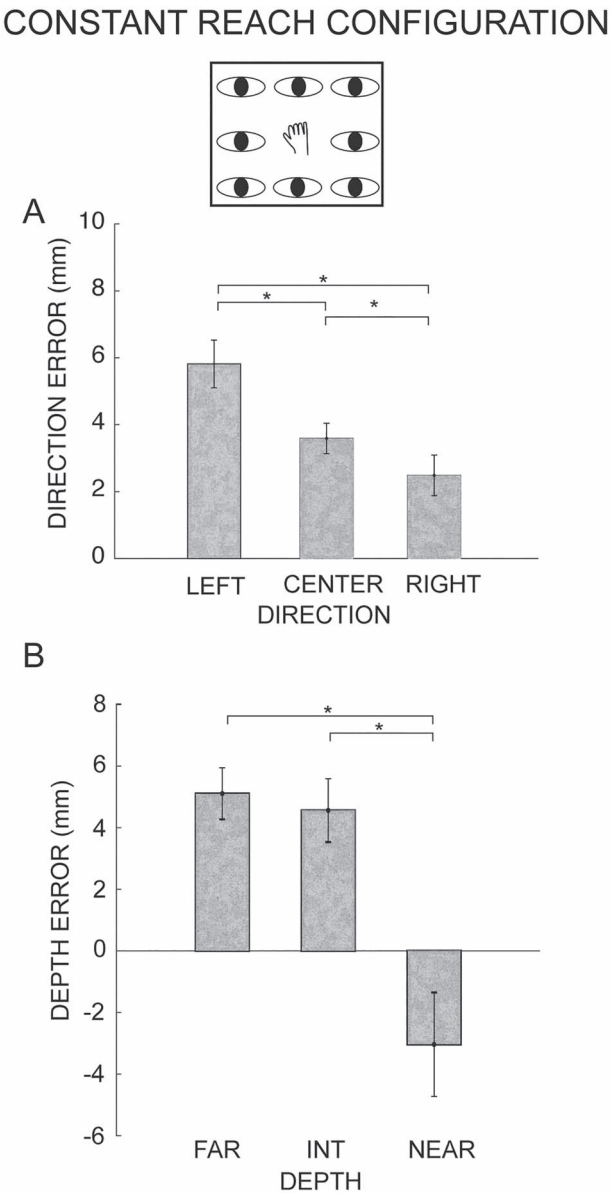

Figure 3. Accuracy in the constant reach configuration. (A) Influence of the direction of the gaze position on direction errors, shown by the distribution of direction errors for reaching movements executed when the gaze was in different directions. Accuracy varied as a function of gaze position. (B) Effect of depth of the gaze position on the depth errors, as shown by the distribution of depth errors for reaching movements executed when the gaze was at different depths (FAR = gaze positions far from the body, INT = intermediate gaze positions, NEAR = gaze positions near to the body). The depth of the gaze position influenced the reach accuracy. Other conventions as in Figure 2.

As Figure 3B illustrates, depth strongly influenced the depth error ($F_{2,28} = 34.9$, $P < 0.001$, partial $\eta^2 = 0.71$), leading to a change in its sign (from negative to positive) when gaze position was held near the body during a central reaching (−3.03 mm ± 1.67), resulting in significantly different values relative to when the gaze was held in the intermediate (4.56 mm ± 0.95; $P < 0.001$) and far target position (5.11 mm ± 0.77; $P < 0.001$), which in turn did not differ from one another ($P = 0.61$). We also found a significant, although nonrelevant, main effect of stimulation time ($F_{1,14} = 8.65$, $P = 0.01$, partial $\eta^2 = 0.38$), with more accurate reaches in the 200-ms trials (1.91 mm ± 0.98) relative to the 100-ms trials (2.50 mm ± 1.06).

Foveal Reach Configuration (Foveal Reaching)

Reach end-point precision

Similarly to the other configurations, spTMS on hV6A did not influence the end-point precision in the Foveal reach configuration (all $F < 2.29$, all $P > 0.11$, all partial $\eta^2 < 0.14$, Supplementary Fig. S2C). The effects of depth and direction on end-point precision, irrespectively of the stimulation, are described in the Supplementary material.

Reach end-point accuracy: direction error

TMS did not influence the direction error (all $F < 0.93$, all $P > 0.4$, all partial $\eta^2 < 0.06$). We observed a strong influence of direction of reaching on end-point accuracy ($F_{2,28} = 10.09$, $P < 0.001$, partial $\eta^2 = 0.42$; Fig. 4A): movements directed to the left space (4.6 mm ± 0.40) were less accurate than movements directed toward the center (3.4 mm ± 0.22; $P = 0.04$) and the right space (2.31 mm ± 0.46; $P < 0.001$), which in turn differ from one another ($P = 0.02$).

Reach end-point accuracy: depth error

We observed a weak borderline effect of stimulation condition by stimulation time ($F_{2,28} = 3.41$, $P = 0.05$, partial $\eta^2 = 0.19$; Fig. 4B and Supplementary Fig. S3C). This was driven by an increased tendency to perform hypometric misreaches in 100-ms trials following V1/V2 stimulation (2.57 mm ± 0.53) relative to sham (1.78 mm ± 0.70; $P = 0.006$) and, even though not strictly significant, to hV6A stimulations (2.07 mm ± 0.61; $P = 0.07$), which in turn did not differ from one another ($P = 0.24$). No significant effect of stimulation was observed in 200-ms trials (all $P > 0.09$). Depth strongly influenced depth errors, irrespective of the stimulation condition and time ($F_{2,28} = 11.57$, $P < 0.001$, partial $\eta^2 = 0.45$, Fig. 4C), with reaches to the farthest targets showing greater hypometric errors (3.14 mm ± 0.75) than intermediate (2.35 mm ± 0.51, $P = 0.04$) and near targets (1.4 mm ± 0.56, $P < 0.001$), which in turn differ from one another ($P = 0.01$).

Discussion

In this study, we demonstrated that spTMS delivered over hV6A affects reaching movements toward nonfoveated targets (peripheral reaching) located far from the participants' body and from the gaze position. Specifically, stimulation of hV6A during motor planning resulted in an unaltered reaching precision but a consistent decrement in endpoint accuracy, with the endpoints shifting in depth toward the gaze (magnetic misreaching in depth). This decrease in accuracy was not accompanied by effects on reaction time nor on movement time, so we can rule out the possibility that a speed/accuracy trade-off occurred in our participants following brain stimulation.

Our stimulation site was located in the medial exposed surface of PPC, anterior to the parieto-occipital sulcus (POs) and medial to the intraparietal sulcus (Fig. 1A), a region that, with different nomenclatures, has been the target of different neuroimaging and TMS studies. In 2008, Culham and coworkers defined the cortical region that included the superior end of the POs and the regions immediately anterior (in the precuneus) and posterior (in the cuneus) to the sulcus as the "SPOC" (Culham et al. 2008). Note that the anterior part of the SPOC

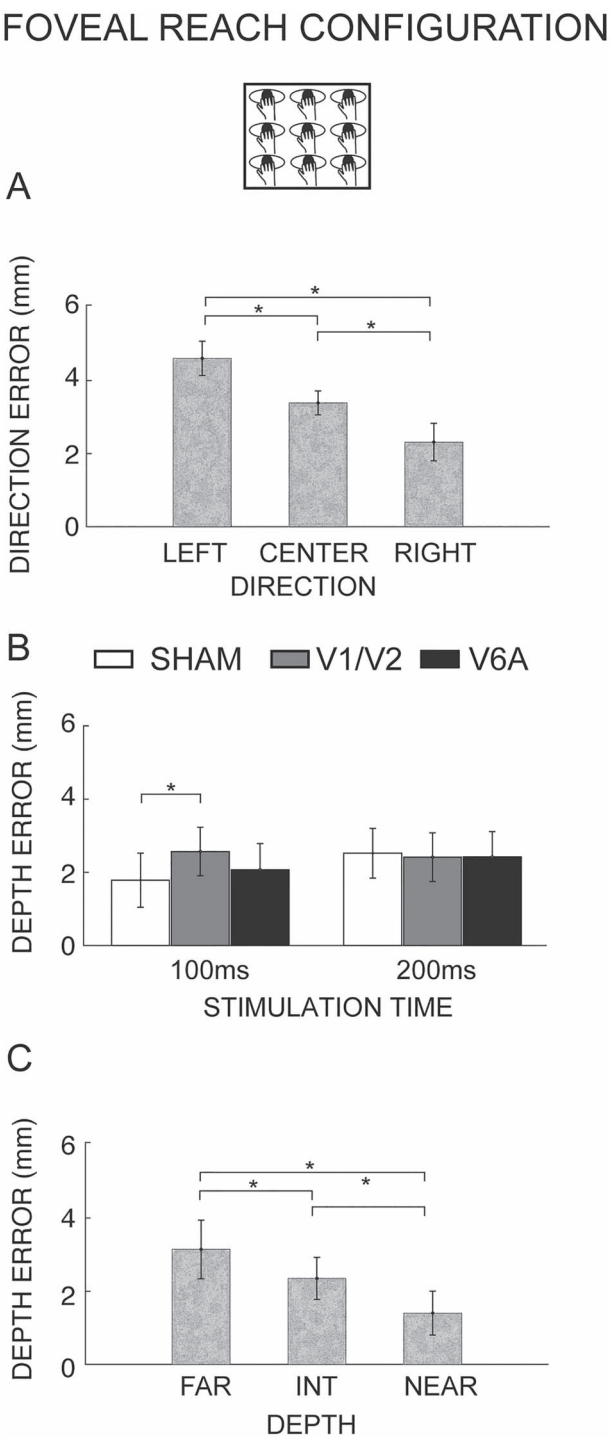

Figure 4. Accuracy in the foveal reach configuration. (*A*) Effect of the direction of reaching on the direction errors, as shown by the distribution of direction errors for reaching movements executed toward targets located in different directions. The direction of foveal reaching influenced the reaching accuracy. (*B*) Distribution of depth errors in 100-ms trials and 200-ms trials in the different stimulation conditions. The stimulation of V1/V2 at 100 ms decreased the reaching accuracy. (*C*) Effect of depth of reaching on the depth errors, as shown by the distribution of depth errors for reaching at different depths. Accuracy of reaching at different depths differed. Other conventions as in Figure 2.

(aSPOC), which roughly corresponds to our stimulation site, likely includes the human homolog of area V6Ad (hV6Ad) (Tosoni et al. 2015). According to Pitzalis et al. (2013), posteriorly and laterally to hV6Ad there is the human homolog of area V6Av and, posterior to it, the human homolog of area V6 (Pitzalis et al. 2015), both regions that were not the focus of our magnetic stimulation. Therefore, according to Pitzalis' lab (Pitzalis et al. 2013; Tosoni et al. 2015), and despite the limited spatial resolution of TMS, we infer that the stimulated area in the present experiment is mostly centered over the hV6Ad. Note that the Talairach coordinates of our stimulation site were the same as those used in another TMS study on hV6A (Ciavarro et al. 2013), and were consistent with those used by Vesia et al. (2010).

Given the high percentage of neurons modulated during reach planning in monkey V6A (Fattori et al. 2005; Hadjidimitrakis, Bertozzi, Breveglieri, Bosco et al. 2014; Santandrea et al. 2018), we applied TMS to the hV6A during the movement planning period, after the Go signal and before the movement onset. The single-pulse protocol was used to finely discriminate the timing of causal involvement of hV6A in movement planning. Indeed, it enabled us to demonstrate that only stimulations delivered 200 ms (but not 100 ms) after the Go signal turned out to be effective. This timing is well in keeping with the peak activation in PPC areas after visual stimulation in a reaching task (Bernier et al. 2009; Fattori et al. 2012). Our results suggest that hV6A elaborates information about the reach plan around 200 ms after the Go signal, that is when target location has presumably been already encoded.

The present results are consistent with the lack of effects in participants' reaching precision observed by Vesia et al. (2010) following hV6A stimulation. Both Vesia et al. (2010) and Ciavarro et al. (2013) found changes in reaching accuracy after hV6A stimulation, similarly to what we found in the present work, but they did not test reaching movements in depth, that instead we did here. Taken together, the magnetic misreaching in depth found in the current study and that in direction found by others (Van Donkelaar and Adams 2005; Vesia et al. 2010; Ciavarro et al. 2013) are consistent with the inability of optic ataxia patients to decouple reach from gaze (Carey et al. 1997; Jackson et al. 2005; Granek et al. 2012). All TMS data demonstrate a causal, crucial role of medial PPC in reaching, as suggested by a plethora of previous correlational studies in both monkeys and humans (Battaglia-Mayer et al. 1998; Pisella et al. 2000; Snyder et al. 2000; Astafiev et al. 2003; Connolly et al. 2003; ; Galletti et al. 2003; Prado et al. 2005; Fernandez-Ruiz et al. 2007; Levy et al. 2007; Culham et al. 2008; Filimon et al. 2009; Cavina-Pratesi, Ietswaart et al. 2010; Vesia et al. 2010, 2013; Vesia and Crawford, 2012; Tosoni et al. 2008; Hadjidimitrakis et al. 2011, 2015; Galletti and Fattori 2018).

Effect of TMS on peripheral and foveal reaching

In our experiment, we asked participants to perform foveal or peripheral reaching using a variety of eye-hand configurations. Surprisingly, despite the high incidence of neurons modulated by the preparation of foveal reaching found in monkey V6A (Fattori et al. 2005; Hadjidimitrakis, Bertozzi, Breveglieri, Bosco et al. 2014), we did not find any effect when TMS was delivered on hV6A during the planning of foveal reaching. On the other hand, we found that TMS over V1/V2 (but not over hV6A) disrupted planning of foveal reaching when stimulation was administered at 100 ms (but not at 200 ms) after the Go signal. These findings suggest that occipital stimulation acts as a masking of visual information when TMS is administered at 100 ms from stimulus

onset, as suggested by previous reports (Amassian et al. 1989; de Graaf et al. 2014). Our findings expand this previous work by showing that interference with visual processing could, in turn, impact motor planning. Moreover, our findings provide evidence of a double dissociation between V1/V2 and hV6A stimulation and show a specific timing of causal involvement of these brain regions in the planning phase of reaching movements, thus ruling out the influence of unspecific effects.

A clear effect of hV6A stimulation on reaching was only observed for peripheral reaching, in agreement with a previous work reporting that medial PPC regions were activated during peripheral, but not during foveal reaching (Prado et al. 2005). The present results also demonstrate that the spTMS over hV6A altered the reach plan only when reaching was directed farther away with respect to the fixation point. In other words, the effect seemed to be influenced not by the peripheral reaching per se, but by the location of reaching target with respect to the fixation point. This means that in hV6A the target of reaching is encoded in a retinal frame of reference, in agreement with functional magnetic resonance imaging (fMRI) results suggesting that medial PPC encodes visual targets in retinal coordinates (Fernandez-Ruiz et al. 2007). However, the present results also show that when the gaze is directed toward the nearest positions and the targets of reaching are located in the central positions (that is, farther than the gaze), the reaching is not affected. In other words, to elicit reaching impairments after virtual lesions of V6A, it is not enough to have the targets of reaching farther than the location of gaze, but they must be also far from the body. This suggests that hV6A encodes the target of reaching in both retinotopic (farther than the gaze) and spatial (far from the body) frames of references. Alternatively, it could be that hV6A is involved in the remapping of visual target information from a retinotopic to a hand-centered reference frame, a process that may occur during the reaction time, as also suggested by a recent paper (Hadjidimitrakis et al. 2020). All these views are well in agreement with the presence in monkey V6A of neurons with visual receptive fields in retinal, spatial, and in mixed retinal-spatial coordinates (Galletti et al. 1993, 1995; Marzocchi et al. 2008; Bosco et al. 2015; Bosco et al. 2016; Hadjidimitrakis, Bertozzi, Breveglieri, Fattori et al. 2014, 2020).

While the PPC is commonly viewed as a sensorimotor interface that merges sensory information to plan goal-directed movements, its functional role is still under debate, with sensory-based accounts of PPC organization on the one hand (Bisley and Mirpour 2019) and motor-based accounts on the other (Andersen and Cui 2009). Remarkably, the impairment that we observed here after TMS may support an alternative view (Medendorp and Heed 2019) which essentially regards the PPC, but also V6A, as a state estimator (Bosco et al. 2010; Grafton, 2010; Shadmehr et al. 2010; Fattori et al. 2017), which evaluates the current state of the world and body that relates to choosing and specifying the most appropriate actions.

Depth versus direction encoding of reach target.

The decreased accuracy of the amplitude of reaching after hV6A magnetic stimulation found in the present study provides a demonstration of the causal involvement of hV6A in the encoding of reaching, in agreement with the stronger effect of depth than of direction of reaching observed in single V6A cells (Hadjidimitrakis, Bertozzi, Breveglieri, Bosco et al. 2014). Another remarkable demonstration of the causal involvement of V6A in the encoding of reaching comes from a previous lesion study in monkeys where V6A was surgically removed (Battaglini et al. 2002; Galletti et al. 2003). The animals were strongly impaired in reaching and grasping pieces of food, particularly in the farthest positions of the peripersonal space. The involvement of V6A in depth encoding has also been suggested in optic ataxia patients, whose cortical lesions likely involved area V6A (Galletti et al. 2003; Karnath and Perenin 2005; Fattori et al. 2017). In these patients, visuomotor deficits stronger in depth than in direction were repeatedly observed, together with specific impairments of arm movements toward targets arranged at different distances from the body (Holmes and Horrax 1919; Baylis and Baylis 2001; Danckert et al. 2009; Cavina-Pratesi, Monaco et al. 2010).

Comparison with other TMS studies

Two studies (Vesia et al. 2010; Ciavarro et al. 2013) that applied TMS over a cortical region similar to our stimulation site, reported impairments in the accuracy (direction error) of reaches. In the present work, we observed a similar effect (Fig. 2A), but it was not specifically related to the stimulation of hV6A. The reasons for this discrepancy between our data and the above-mentioned studies can be manifold. First, there are differences in the task we used. We employed a visually -guided reaching task, providing the participant with visual information about target location during TMS, whereas the other two studies used a memory-guided reaching (Vesia et al. 2010; Ciavarro et al. 2013). The effect observed in Vesia's and Ciavarro's experiments and the lack of this effect when providing visual information (current study) suggests that the involvement of V6A in reach planning is more marked when visual information is not available. The strong activations of many V6A cells during arm reaching in the dark and the inhibition of several of them in the light (Bosco et al. 2010) agree with this view. Another possible factor that can contribute to the observed discrepancy is the different TMS paradigms: while in Vesia's and Ciavarro's studies a repetitive stimulation was administered (Vesia et al. 2010; Ciavarro et al. 2013), here we used a single pulse para digm. It is possible that the directional impairments observed by Vesia and Ciavarro are caused by the greater interference with hV6A obtained by using trains of TMS pulses instead of a single pulse.

Previous works demonstrated that V6A neurons receive a strong proprioceptive input from the arms (Breveglieri et al. 2002; Gamberini et al. 2011, 2018) and that the proprioceptive input during reaching is stronger in the depth dimension compared to direction (Vindras et al. 1998; Van Beers et al. 2004; Apker et al. 2010). This could explain why, in our experimental conditions, the interference with V6A increased depth errors rather than direction errors.

Our study shows that the accuracy of visually guided reaching movements in depth is disrupted by hV6A stimulation but not by V1/V2 stimulation. Although site-specific, such effect could be not site-limited. Indeed, it is known that TMS affects neural activity not only locally, but also remote interconnected region (Siebner et al. 2009; Avenanti et al. 2013; Valchev et al. 2015). Thus, it is possible that TMS-induced excitation due to hV6A targeting might have spread along other nodes of the dorsomedial stream (Galletti and Fattori 2018) and these nodes might have contributed to the observed changes in reaching performance. Future studies could combine TMS perturbation with EEG or fMRI (Bestmann et al. 2008; Zanon et al. 2018) to monitor the extension of the neural network altered by hV6A stimulation during motor performance.

Area V6A and the online control of reaching

Monkey V6A contains visual cells with a short latency of activation (about 80 ms)(Kutz et al. 2003; Fattori et al. 2012). This visual information is directly transferred from V6A to the premotor cortex (Matelli et al. 1998; Shipp et al. 1998; Galletti et al. 2004), likely to feed motor centers with vision-for-action information (Fattori et al. 2012). The short latency of visual information coming from V6A is compatible with the fast motor response of an automatic system that performs unconscious online corrections of the direction of movement in the case of unexpected target jumps after movement onset (Goodale et al. 1986; Pélisson et al. 1986; Paulignan et al. 1991; Prablanc and Martin 1992). The presence in V6A of many neurons modulated during reaching execution (Fattori et al. 2001, 2005, 2017; Bosco et al. 2010; Hadjidimitrakis, Bertozzi, Breveglieri, Fattori et al. 2014) as well as by visual stimulation (Gamberini et al. 2011; Fattori et al. 2012; Breveglieri et al. 2015) suggests that this area could participate in the online monitoring of arm movement during reaching and could be involved in the correction of ongoing arm movement in case of perturbation of reach target location (Galletti et al. 2003; Rizzolatti and Matelli 2003; Galletti and Fattori 2018). However, despite the intriguing above-reported suggestion, no study to date has demonstrated the presence of V6A neurons modulated by changes in reaching trajectory evoked by sudden target displacements. Conversely, such a type of neurons have been reported in the lateral PPC (specifically, in the lateral part of area PE) (Archambault et al. 2009, 2015; Battaglia-Mayer et al. 2013), and in agreement with these data, TMS on the lateral PPC disrupted the path corrections that normally occur in response to target jumps (Desmurget et al. 1999 Reichenbach et al. 2011; Reichenbach et al. 2014). In other words, previous data suggest that the lateral PPC is involved in the online correction of arm movements, whereas the present findings indicate that the medial PPC is involved in the planning of movement and/or in remapping target information between different reference frames. Whether V6A is also causally involved in the online control of reaching movement is a question that remains open, because to check this point one should apply TMS during the movement time instead of reaction time as in the present case. Further experiments with this goal are needed to clarify this point.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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