Modulation of motor control in saccadic behaviors by TMS over the posterior parietal cortex

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Liang WK, Juan CH. Modulation of motor control in saccadic behaviors by TMS over the posterior parietal cortex. J Neurophysiol 108: 741–752, 2012. First published May 2, 2012; doi:10.1152/jn.01135.2011.—The right posterior parietal cortex (rPPC) has been found to be critical in shaping visual selection and distractor-induced saccade curvature in the context of predictive as well as nonpredictive visual cues by means of transcranial magnetic stimulation (TMS) interference. However, the dynamic details of how distractor-induced saccade curvatures are affected by rPPC TMS have not yet been investigated. This study aimed to elucidate the key dynamic properties that cause saccades to curve away from distractors with different degrees of curvature in various TMS and target predictability conditions. Stochastic optimal feedback control theory was used to model the dynamics of the TMS saccade data. This allowed estimation of torques, which was used to identify the critical dynamic mechanisms producing saccade curvature. The critical mechanisms of distractor-induced saccade curvatures were found to be the motor commands and torques in the transverse direction. When an unpredictable saccade target occurred with rPPC TMS, there was an initial period of greater distractor-induced torque toward the side opposite the distractor in the transverse direction, immediately followed by a relatively long period of recovery torque that brought the deviated trace back toward the target. The results imply that the mechanisms of distractor-induced saccade curvature may be comprised of two mechanisms: the first causing the initial deviation and the second bringing the deviated trace back toward the target. The pattern of the initial torque in the transverse direction revealed the former mechanism. Conversely, the later mechanism could be well explained as a consequence of the control policy in this model. To summarize, rPPC TMS increased the initial torque away from the distractor as well as the recovery torque toward the target.

transcranial magnetic stimulation; right posterior parietal cortex; eye movements; saccade curvature; stochastic optimal feedback control theory

IN AN OVERT VISUAL SEARCH TASK, saccadic eye movements, especially when distractors are presented along with the targets, often reveal important information regarding attention capture not only from their latencies but also from their trajectories (e.g., Sheliga et al. 1994; McPeek et al. 2003). To quantify how saccade trajectories are affected by distractors, saccade curvature has been investigated extensively in previous research (e.g., Sheliga et al. 1995; van der Stigchel et al. 2006; Walker and McSorley 2006). However, there are several essential dynamic details that cannot be obtained by merely computing saccade curvatures, such as the timing of deviation, motor command, and torque. Many transcranial magnetic stimulation (TMS) studies have revealed the critical roles of the posterior parietal cortex (PPC) in the control of visuospatial and visuomotor processes (e.g., Walsh et al. 1999; Rushworth et al. 2001; Ellison et al. 2003; Ellison and Cowey 2007; Silvanto et al. 2009; Tseng et al. 2010; for a review, see Rushworth and Taylor 2006). However, the characteristics of TMS effects on saccadic behaviors remain unclear. A recent study by Chao and colleagues (2011) used right PPC (rPPC) TMS to investigate the role of the rPPC in shaping saccade curvatures in the context of predictable and unpredictable cues, illustrating three important aspects of TMS modulation of saccade curvatures. The first aspect is that when TMS is applied to the rPPC, saccade latencies generally increased (e.g., Muri et al. 1996; Kapoula et al. 2001). This elevation of saccade latencies revealed that the brain paid a greater cost to prepare saccades under rPPC TMS. The second aspect refers to the magnitude of saccade curvature away from the distractor, which increased under rPPC TMS only when the target location was unpredictable. This change of saccade curvature reflected the dynamic competition between target selection and distractor suppression that was altered under rPPC TMS. The third aspect unveils the association between the rPPC-TMS-prolonged saccade latency and increased degrees of saccade curvature, which occurs only when target was unpredictable. Because little is understood about the role of the rPPC in planning saccades in the presence of a distractor, the present study is an essential extension of the 2011 TMS study by Chao et al. (2011) to elaborate on the dynamic properties of saccadic eye movements when affected by TMS as well as the role of the rPPC in these movements.

To further understand the mechanisms of attention underlying saccade trajectories, a model that is able to reveal both motor control as well as the state of the eye is needed to estimate the dynamic properties underlying these trajectories. Because there are data and theories suggesting that saccadic motor commands benefit from an internal feedback system that optimizes motor commands as well as monitoring their consequences (Chen-Harris et al. 2008), the model used in the present study considered both the basic dynamics of the eye movements as well as the online correction of motor commands. For these reasons, the stochastic optimal feedback control theory (SOFCT) was chosen to be the model applied to the TMS eye movement data.

The SOFCT is based on Bellman’s optimality principle (Bellman 1957) with the Kalman filter (Kalman 1960) to estimate the state of the eye. To apply the SOFCT to TMS eye movement data, the eye was modeled as a linear system with signal-dependent noise produced by motor commands (which appears to be the case for biological systems). Furthermore, sensory observations, which also suffer from noise, play a role in feedback. Technically, this theory is a close-loop optimal control problem that has been solved iteratively by Todorov (2002, 2005). Todorov’s solution to this problem gives esti-
mates of the relationship between the motor commands and the state of the eye, that is, the control policy. Consequently, once the control policy is determined, the motor command may be estimated from the state of the eye. In the present study, the SOFCT was used to map the saccade trajectory to derive a relatively more internal physical quantity (torque) as well as an intrinsic index of brain effort (the motor command).

The results from the model suggest that the critical mechanisms for producing saccade curvature are the motor commands along with the consequential torques in the transverse direction (i.e., the direction that is perpendicular to the direction of saccade target). When participants were presented with an unpredictable saccade target with the TMS delivered over the rPPC, there was an initial period of greater distractor-induced torque toward the side opposite to the distractor in the transverse direction. Immediately after this, there was a series of relatively large recovery torques that brought the deviated trace back to the target. Although there are hidden mechanisms that generated the initial transverse torque causing the saccade to deviate away from the distractor in the very beginning of the saccade, the control policy may transform a deviated state into motor commands along with the consequential torques that drove the saccade back toward the target location by way of least cost. Furthermore, we provide a correlation analysis to confirm the relation between saccade curvature and the transverse torque estimated by SOFCT.

In the present study, both saccade curvature and motor control, as estimated by SOFCT, were used to investigate the role of the rPPC in distractor modulation. A previous study (Chao et al. 2011) has shown an association between the rPPC-TMS-induced increase in saccade latency and increase in saccade curvature, which only occurs when target is unpredictable. Here, further clarification is offered, from the perspectives of saccade curvature and motor control, on the origin of the increase of distractor-induced saccade curvature under rPPC TMS when the target is unpredictable. The results demonstrate that the origin of the increased saccade curvature in the unpredictable condition was not merely caused by the rPPC-TMS-induced increase in saccade latency but also by rPPC TMS itself.

MATERIALS AND METHODS

Experiment design and procedures. The experiment used a within-subject design. Eleven participants (4 men and 7 women, age: 20–26 yr old, mean age: 21.6 yr) took part in the experiment across three conditions (rPPC TMS, no TMS, and M1 TMS, where M1 TMS was delivered over right primary motor cortex). All participants were randomly chosen from a pool of undergraduate students from the National Central University. All had normal or corrected to normal vision and gave informed consent before the experiment. Participants received monetary reward upon the completion of the experiment. The motor threshold (Stokes et al. 2005) of each subject was recorded and was as follows: 67%, 69%, 65%, 66%, 66%, 60%, 64%, 56%, 65%, 54%, and 58% of maximal stimulator output (2.57 T). After the experiment, none of the subjects reported any negative side effects from either TMS sessions (rPPC TMS and M1 TMS). The experiments were approved by Institutional Review Board of the Chang-Gung Memorial Hospital (Taoyuan, Taiwan).

Stimuli were presented on a 19-in. CRT monitor with a resolution of 1,024 × 768 pixels and a vertical refresh rate of 100 Hz. Participants sat 85 cm in front of the monitor, which was positioned at eye level. The position of the left eye was recorded using an EyeLink II tracker (SR Research, Mississauga, ON, Canada) with a sampling rate of 500 Hz. A nine-point calibration was carried out in every participant before the formal collection of data. Saccades were defined by a significant elevation in eye movement velocity (>30°/s) and acceleration (>8,000°/s²).

The stimuli used in the experiment are shown in Fig. 1. There were four possible positions for targets and distractors (cf. 8 positions in Walker et al. 2006). Target as well as distractor positions were 10° away from the fixation. The target (a cross), distractor (an unfilled circle), and fixation (a diamond) were all 1° in size. Target positions were constrained to four locations on the diagonal (oblique) axes. When a distractor was present, it appeared either clockwise or counterclockwise immediately adjacent to the target location. The number of trials with a distractor in the clockwise direction was the same as that in the counterclockwise direction.

The entire experiment consisted of three conditions: rPPC TMS, no TMS, and M1 TMS. All conditions were within subject and were run on 3 different days to avoid the possibility of any lingering TMS effect from the previous TMS session. The materials, stimuli, and procedures were identical across all conditions. Thus, the only difference between these three conditions was the TMS site. The orders of the rPPC TMS and no TMS conditions were counterbalanced between each of the first 10 participants. The M1 TMS condition was added as another control to ensure the specificity of any TMS effects over the rPPC and was always run after the other two conditions.

Within each condition (rPPC TMS, no TMS, and M1 TMS), there were two blocks of trials: one block for the predictable condition and one block for the unpredictable condition. The order of the two blocks within each TMS condition along with the order of no TMS and rPPC TMS conditions were counterbalanced across subjects. In the rPPC TMS and M1 TMS conditions, theta burst TMS was applied at the beginning of both blocks [“theta burst” is a stimulation pattern in which 3–5 pulses of stimulation are given at 50–100 Hz, repeated every 200 ms (for more technical details, see Huang et al. 2005)]. Compared with single-pulse stimulation, the theta burst TMS effect lasts longer (~20 min) and therefore can induce lasting disruptive effects on the stimulated region (e.g., Liu et al. 2011; Chang et al. in press). Participants then rested for 5 min (Hubl et al. 2008) before participating in the formal experiment. The two blocks were also separated by 1 h of rest for the participants. Each block lasted ~13 min. This ensured that the experiment length did not exceed the duration of the theta burst TMS effect (Huang et al. 2005).

Each block began with 40 practice trials followed by 120 formal trials. This was based on our pilot study and previous experiences to avoid outlier data due to unfamiliarity with the task. The 120 formal trials consisted of 40 no distractor trials and 80 distractor trials. The saccade curvatures from the no distractor trials served as a baseline for determining the curvatures from the distractor trials.

![Fig. 1. Experimental paradigm. The experiment consisted of two blocks. In the unpredictable block, a neutral cue (hourglass) was provided, whereas in the predictable block a directionally specific cue (arrow) toward the upcoming target location (the “x”) was provided.](http://jn.physiology.org/10.1152/jn.01135.2011)
Each trial started with a fixation (a diamond in block 1 and a complex diamond in block 2) for 300 ms followed either by a directionless cue (an hourglass, condition 1) or a directional cue (an arrow, condition 2). The directional cue was 100% valid (Walker et al. 2006). After a random delay ranging from 800 to 1,300 ms, the target and distractor appeared simultaneously while the cue was still present. Participants were instructed to fixate at the center fixation until the target onset and make a saccade to the target within 1 s.

In all TMS conditions (rPPC TMS and M1 TMS), theta TMS was applied before the formal experiment. It has been shown that theta TMS can suppress motor evoked potentials in the primary motor cortex for >20 min (Huang et al. 2005). Theta TMS can also selectively excite or inhibit neural activities of different brain regions (Silvanto et al. 2007), making it a suitable method for studying higher cognitive functions (e.g., Nyffeler et al. 2006; Silvanto et al. 2007). Various neuropsychological, neuroimaging, and TMS studies have suggested that the rPPC is involved in the spatial search for conjunction items (Friedman-Hill et al. 1995; Nobre et al. 2003). In the present study, TMS was delivered over the rPPC in the expectation of changing the weights of target-distractor representation as well as the degree of distractor suppression in saccade preparation, as suggested by McPeek and colleagues (McPeek et al. 2006; see also Muri et al. 1996). We used a Magstim Super-Rapid Stimulator and a figure-eight coil to deliver rPPC TMS. The site of theta TMS stimulation was point P4 on the 10-20 electroencephalograph coordinate system (Mevorach et al. 2006). The stimulation site was also confirmed with subjects’ structural MRI with the BrainSight system (Rogue Research, Montreal, QC, Canada). Our participants wore goggles with a tracker attached, enabling them to be coregistered with their structural image using a mounted Polaris infrared tracking system (Northern Digital, Waterloo, ON, Canada), subsequently allowing the skull point overlying the stimulated region to be identified. The site was in the vicinity of rPPC areas used for the investigation of the functional role of the PPC in visual search tasks (e.g., Ashbridge et al. 1997; Ellison et al. 2003, 2007; Kalla et al. 2008; Beck et al. 2006; Tseng et al. 2010), which corresponds to point P4 (right parietal) on the 10-20 electroencephalography coordinate system. Participants received three pulses of stimulation given at 50 Hz repeated starting every 200 ms for 20 s at 40% of maximum output (40% of the maximum output of 2 T) (Huang et al. 2005), which was well below each individual participants’ motor threshold (the lowest of which was 53%)

A fixed stimulation level was used because it has proven successful and replicable in many studies and over a wide range of tasks (e.g., Ashbridge et al. 1997; Rushworth et al. 2002; Muggleton et al. 2003; Ellison and Cowey 2007; Hung et al. 2005; Kalla et al. 2008; Chen et al. 2009; Muggleton et al. 2010) and because motor cortex excitability does not provide a good guide to TMS thresholds in other cortical areas (Stewart et al. 2001).

Modeling: Motor control of saccades

To apply the SOFCT to the eye movement TMS data, the oculomotor plant was modeled as a linear system with signal-dependent noise (Harris et al. 1998) as follows:

\[
\begin{align*}
\dot{x}^{(k)} &= A_k x^{(k)} + B_k [u^{(k)} + \epsilon_k] \\
\dot{y}^{(k)} &= H_k x^{(k)} + w^{(k)}
\end{align*}
\]

where \(x^{(k)} = [e_x, \dot{e}_x, e_y, \dot{e}_y, g_x, g_y]^T\) is the two-dimensional state of the eye at time \(k\) [the \(x, y\) components of position (\(e\)), velocity (\(\dot{e}\)), and torque (\(f\)) followed by the target position (\(p\))], \(y^{(k)} = [m_x, m_y, \dot{m}_x, \dot{m}_y]^T\) is the observation [position (\(m\)) and velocity (\(\dot{m}\)), and \(u^{(k)} = [u_x, u_y]^T\) is the motor command that causes a change in \(x^{(k)}\). \(T\) denotes the transpose, and \(\epsilon_k\) is signal-dependent noise. The observation \(y^{(k)}\) obtained from the experimental data, is related to the hidden states \(x^{(k)}\) with the measurement noise \(w^{(k)} \sim \mathcal{N}(0, Q)_k\), where \(Q\) denotes normal distribution, and \(Q\) is the covariance matrix. The discrete system matrices \((A_k, B_k, A_k, H_k)\) were derived from a continuous-form simple model describing the dynamics of the eye (Fig. 2), along with a simple muscle model transforming motor commands into torques (Shadmehr et al. 2011), as follows:

\[
\begin{align*}
\dot{x} &= \frac{k}{m} x - \frac{b}{m} \dot{x} + \frac{1}{m} f \\
\alpha \frac{df}{dt} + \alpha \dot{f} &= u
\end{align*}
\]

where \(\dot{x}\) is the acceleration, \(x\) is the velocity, \(b\) is the damping coefficient, \(\alpha\) is time, and \(\alpha\) and \(\alpha\) define the relation between the torque and the rate of change of the torque caused by the motor command, \(u\). \(e^{(k)}\) could be expressed as normally distributed scalar random variables \(\phi_1\) and \(\phi_2\) as follows:

\[
\begin{align*}
\phi_i &\sim \mathcal{N}(0, 1) \\
C_1 &= \begin{bmatrix} c_1 & 0 \\ 0 & 0 \end{bmatrix} \\
C_2 &= \begin{bmatrix} 0 & 0 \\ 0 & c_2 \end{bmatrix} \\
e^{(k)}_i &= \sum C_i u^{(k)}
\end{align*}
\]

where \(i = (1, 2)\), \(C_1\) and \(C_2\), constructed with the elements \(c_1\) and \(c_2\), respectively, are used to express the covariances \(\sum C_i uu^T C_i\). The inference of the modeling is the estimates of the motor commands \(u^{(0)}, u^{(1)}, \ldots, u^{(p-1)}\) (where \(p\) is the previous time point) that minimize the following cost-to-go function \(J^{(k)}\) (Todorov 2005) at each time point \(k = 0(p-1)\):

\[
f^{(k)} = u^{(k)}T_L^{(k)} u^{(k)} + x^{(k)}T_x^{(k)} x^{(k)} + E^{(k+1)} x^{(k+1)} x^{(k)} + H^{(k+1)} x^{(k+1)} x^{(k)}
\]

where \(T^{(k)}\) is the control cost matrix, \(T_x^{(k)}\) is the state cost matrix, and \(E^{(k)}\) denotes the expected value. The state estimates \(\hat{x}^{(k)}\) along with the motor command estimates \(\hat{u}^{(k)}\) under the minimum cost constraint are as follows:

\[
\begin{align*}
\hat{x}^{(k+1)} &= A \hat{x}^{(k)} + B [\hat{u}^{(k)} + \hat{e}^{(k)}] \\
\hat{u}^{(k)} &= -G^{(k)} \hat{x}^{(k)}
\end{align*}
\]

where \(K^{(k)}\) is the Kalman filter, and \(G^{(k)}\) is the control policy derived from the following relationships:
The procedure to obtain control policy \( G^{(k)} \) may be summarized in three parts: 1) set \( W^{(0)} = \Psi^{(0)} \) together with \( W^{(0)} = 0 \) for the last time point, 2) estimate control policy \( \hat{G}^{(k-1)} \) by minimizing the cost-to-go function at previous time point \((p - 1)\), and 3) calculate recursively backward step by step to the first time point. The sequences \( \Psi^{(k)} \) and \( W^{(k)} \) are computed iteratively until both of them converge (Todorov 2005).

**Coordinate system and saccade curvature.** In all analyses in the present study, the coordinate system of the state \( x^{(k)} \) as well as the motor command \( u^{(k)} \) was rotated such that the new \( x\)-axis was in the direction of the saccade target. Consequently, the new \( y\)-axis was in the direction perpendicular to the new \( x\)-axis. The two aforementioned directions, the new \( x\)-axis as well as the new \( y\)-axis, shall simply be referred to as the radial direction and the transverse direction, respectively. The purpose of this coordinate system rotation is to see the dynamic properties that cause curvatures toward or away from the distractor, that is, to decompose the dynamic effects of the target and the distractor. Accordingly, the measurements \( y^{(k)} \) as well as the target position \((g_x, g_y)\) were transformed to the new coordinate system in the same manner.

Instead of using the conventional definitions of curvature (Van der Stigchel et al. 2006), the “slope curvature” (Chen-Harris et al. 2008), being dimensionless and scale invariant with zero scaling dimension, was chosen as the measure of curvature because it was related to the model inference of the current study (see the correlation analysis in Kapoula et al. 2005; Yang and Kapoula 2004). To ensure that there were no effects of visual field difference in this study, analysis was performed both on saccade latency and saccade curvature. The results of three-way (visual field: left/right, TMS: no TMS/rPPC TMS/M1 TMS, target predictability: unpredictable/predictable) ANOVAs both on saccade latency...
and saccade curvature showed no significant main effects of visual field and no interactions between visual field and either of the other two factors (all visual field-related $P$ values were $>0.25$). Because no difference was found between the left and right visual fields, data from both were combined for subsequent analyses. In addition, in the following analyses, all saccade trajectories were reflected to the first quadrant. Furthermore, trials with a distractor at the counterclockwise direction were mirrored with respect to the diagonal axis (target) such that the distractor was at the clockwise direction in all trials.

**Saccade curvature.** The grand averaged distractor-induced saccade curvature of each condition is shown in Fig. 4. Two-way repeated measures ANOVA was performed to investigate whether TMS and target predictability had an effect on saccade curvature. The results showed a significant main effect of TMS [$F_{(2,20)} = 8.179, P < 0.001$] but no effect of predictability [$F_{(1,10)} = 0.23, P > 0.05$], with an interaction between TMS and predictability [$F_{(2,20)} = 6.385, P < 0.01$]. When the target was unpredictable, post hoc tests showed saccade curvatures from the rPPC TMS condition were significantly more away from distractor than both no TMS condition and M1 TMS condition ($P < 0.05$, Bonferroni adjusted). However, this rPPC TMS effect was not observed when the target was predictable. Within the rPPC TMS condition, the curvatures for the unpredictable condition were significantly more negative (away from the distractor) than the predictable condition ($P < 0.001$).

The development of saccade curvature over time of all distractor conditions is shown in Fig. 5. In this analysis, saccades of each condition were divided into five groups (bins) based on their saccade latencies (Mulckhuyse et al. 2009), with each bin containing ~20% of saccades for each participant. Three-way repeated measures ANOVA was conducted to investigate the effects of TMS (three levels), target predictability (two levels), and bins (five levels) on saccade curvature. There was a significant main effect of TMS [$F_{(2,20)} = 7.952, P < 0.01$] and bins [$F_{(4,40)} = 5.877, P < 0.01$] but no effect of target predictability [$F_{(1,10)} = 0.26, P > 0.05$]. Furthermore, a significant interaction between TMS and target predictability [$F_{(2,20)} = 6.303, P < 0.01$] was also observed. The main effect of bins, with an absence of significant interaction, reveals that there may be a general tendency of curvature development over saccade latency. Post hoc simple ANOVA showed a significant effect of bins both within the rPPC TMS-unpredictable condition ($P < 0.05$) and M1 TMS-unpredictable condition ($P < 0.05$). Error bars indicate SEs.

![Fig. 4. Saccade curvatures. The curvature is described as the slope of the fourth segment minus the slope of the first segment of saccade trace. Negative values indicated that the traces curved away from the distractors (at the negative side of the transverse direction). Right posterirol parietal cortex (rPPC) transcranial magnetic stimulation (TMS) increased the magnitude of curvature away from the distractor significantly when the target was unpredictable, thus causing a strong interaction between TMS and predictability. M1 TMS, TMS delivered over the right primary motor cortex. Error bars indicate SEs.](http://jn.physiology.org/)

**Fig. 4. Development of saccade curvature over time (bins of saccade latency).** The negative slope curvature of each distractor condition indicates “away from the distractor.” Besides TMS, there was a significant main effect of bins as well. Post hoc simple ANOVA showed a significant effect of bins in both the rPPC TMS-unpredictable condition ($P < 0.05$) and M1 TMS-unpredictable condition ($P < 0.05$). Error bars indicate SEs.
condition. This finding reveals that the prolongation of saccade latency by rPPC TMS is not a partial but a broad effect, despite target predictability.

**Modeling inferences.** The SOFCT was applied to the eye movement data, with the mean trajectory and velocity of each subject of each condition (TMS \times predictability) serving as the observations (feedback). The grand averages of the estimates of eye states as well as motor commands are shown in Fig. 6A. In the radial direction, the velocities, torques, and motor commands (first to third columns) of all conditions appeared similar. Conversely, in the transverse direction, clear differences between conditions could be observed. The sixth column of Fig. 6A shows the transverse motor commands between ~5 and 35 ms as all negative (the same as the direction of the distractor), that is, positive transverse motor commands only appeared during a small initial period (<5 ms) and at a final stage of the saccade (>35 ms). However, the muscle model (Eq. 3), transforming motor commands into torque, provided a relatively longer initial period (~15 ms) of positive transverse torque that served as the driving force of deviation away from the distractor. In general, the time course of torques showed a phase delay relative to the motor commands. The fifth column of Fig. 6A shows the transverse torques of all conditions. Among them, the rPPC TMS-uncontrollable condition showed the greatest initial torque and thus deviated the most away from the distractor. The rPPC TMS-uncontrollable condition also revealed the greatest recovery torque, which played the role of driving the eye back toward the target.

The estimates of eye states and motor commands at each time point were further tested using repeated-measures ANOVA, followed by post hoc testing with simple ANOVA and paired t-tests. To avoid the false positives from multiple comparisons, a false discovery rate (FDR) controlling procedure (Benjamini and Hochberg 1995) was applied to this analysis at the threshold q* < 0.05. In Fig. 6, B and C, the blue line indicates t-values for paired t-tests or f-values for ANOVAs. In addition, the t-value or f-value of P = 0.05 is shown with a dashed red line, whereas the FDR mask of q* < 0.05 is shown by yellow regions. In the following, if not specified, an effect is recognized as "significant" when its P value was <0.05 with FDR control q* < 0.05. The results of two-way repeated measures ANOVA are shown in Fig. 6B to investigate the effects of TMS (three levels) and target predictability (two levels) on eye states as well as motor commands. As shown in Fig. 6B, there were significant regions of interaction between TMS and target predictability in the transverse velocity, torque, and motor command. There were also significant TMS main effects on the velocity from 1 to 14 ms in the transverse direction. As expected, there was not any main effect of or interaction between eye states and motor commands in the radial direction. Figure 6C shows the results of post hoc tests. Simple ANOVA for the TMS effect in the unpredictable condition revealed that 1) for transverse velocity, there were significant TMS effects from 3 to 16 ms and from 32 to 52 ms; 2) for transverse torque, the significant TMS effects were during 3~6 ms as well as 19~28 ms; and 3) for transverse motor command, the period between 9 and 22 ms showed significant TMS effects. To further identify the TMS effect, paired t-tests were conducted on each pair of TMS conditions in the unpredictable condition. The paired t-tests between rPPC TMS and no TMS conditions (Fig. 6C, rPPC TMS-no TMS row) in the transverse velocity, torque, and motor command showed significant regions that were approximately the same as the associated simple ANOVA. Furthermore, the sign of t-values showed the direction of the difference between the rPPC TMS and no TMS conditions. There was no significant effect in the M1 TMS-no TMS paired t-test, whereas the rPPC TMS-M1 TMS paired t-test achieved the 0.05 level of significance without correction of FDR in the same regions. Since post hoc simple ANOVA for TMS effect in the predictable condition (Fig. 6C, TMS effect in pred., simple ANOVA row) showed no significant effect in any eye state or for any motor command, no further post hoc tests were needed. The results of paired t-tests between the unpredictable and predictable conditions in each TMS condition are shown at the bottom of Fig. 6C. Among them, the significant differences between the unpredictable and predictable conditions only appeared within the rPPC TMS condition.

To investigate the critical time regions shaping the saccade deviation as well as the saccade curvature, the above samples of transverse torque of no TMS conditions were concatenated to one sample. Figure 7 shows the three regions that violated the null hypothesis in a one-sample t-test (P < 0.01 with FDR control q* < 0.01). The first significant region (3~6 ms) of transverse torque was identified as the "initial torque," and the second significant region (23~36 ms) of transverse torque was recognized as the "recovery torque" in the following discussion. The "mean initial torque" or "mean recovery torque" denotes the transverse torque averaging over its related time region. The third significant region is apparently related to the stopping of the saccade, which was not of interest in this study.

Analogous to the results in Saccade curvature, the SOFCT was applied to the five-bin-partitioned eye movement data (based on saccade latencies of each subject), with the mean trajectory and velocity of each subject of each condition (TMS \times predictability \times bins) serving as the feedback. Since the importance of eye states and motor command along the transverse direction has been validated in the previous analysis, here we merely demonstrate the estimates of transverse torque in each condition. Figure 8 shows the grand averaged transverse torque of each bin within each TMS \times predictability condition. In the rPPC TMS condition when target was unpredictable, the magnitude of recovery torque in the fourth bin showed a 5~7-ms period significantly larger than the other bins (P < 0.05, uncorrected) with the exception of the second bin. Similar differences were also observed between the fifth bin and other bins in the M1 TMS condition when target was unpredictable, but the periods of significance (3~4 ms) were in general shorter than those in the rPPC TMS condition. These subtle significances were consistent with the preceding analysis on saccade curvature but did not survive under FDR correction and are not shown in together with the grand averaged transverse torques in Fig. 8.

The mean initial torque as well as the mean recovery torque of each trajectories in the TMS \times predictability \times bins samples were used to test the correlations between curvature, deviation, initial torque, and recovery torque. Table 1 shows the correlation coefficients returning by the correlation analysis (all correlations were significant, P < 10^{-12}). The correlation coefficient was defined as \( R_{ij} = C(i,j)\sqrt{C(i,i)\times C(j,j)} \), where C is the covariance matrix. Among these were the correlation factor between slope curvature and mean recovery torque, which achieved 0.826^*_{0.032} (where "*" and "^*" indicate the 95% confidence interval bounds) as well as the
A: model results of all distractor conditions (from left to right: modeled radial velocity, radial torque, radial motor command, modeled transverse velocity, transverse torque, and transverse motor command). The critical mechanism that caused saccades curve away from the distractor was the motor command and the torque in the transverse direction (sixth column and fifth column, respectively). In the fifth column, the rPPC TMS-unpredictable condition indicated the greatest initial torque and therefore deviated most away from the distractor. The rPPC TMS-unpredictable condition also showed the greatest recovery torque driving the eyes back toward the target location and thus curved most away from the distractor.

B: statistical results of model estimates (two-way repeated-measures ANOVA). The blue line shows $f$-values. The dashed red line indicates the $f$-value of $P/1000 = 0.05$, and the yellow regions indicates the false discovery rate (FDR) mask of $q^* < 0.05$. There were multiple significant regions of interaction (third row) between TMS and target predictability in the transverse velocity, torque, and motor command.

C: post hoc simple ANOVA and paired $t$-test results. The blue line shows $f$-values (simple ANOVA) or $t$-values (paired $t$-test). The dashed red line indicates the $f$-value or $t$-value of $P = 0.05$, and the yellow regions indicates the false discovery rate (FDR) mask of $q^* < 0.05$. The TMS effects in the unpredictable condition (first row) revealed multiple significant regions for velocity, torque, and motor command. Paired $t$-tests between rPPC TMS and no TMS conditions in the unpredictable condition (second row) as well as paired $t$-tests between unpredictable and predictable conditions in the rPPC TMS condition (seventh row) showed multiple significant differences in the transverse direction.
correlation factor between initial deviation [slope (S1)] and mean initial torque, which achieved 0.766
0.048
0.041. These results revealed that the slope curvature was highly correlated to the mean recovery torque and the initial deviation [slope (S1)] was correlated to the initial torque. When we compared the results shown in Fig. 8 with Fig. 5, the recovery torque showed an analogous time development to saccade curvature.

Clarification on the origin of increased saccade curvature. The results of curvature development over time in the unpredictable condition, from Saccade curvature, may need further clarification to exclude the possibility that the increased saccade curvature was merely caused by the increased saccade latency in the rPPC TMS condition. To test this possibility in the unpredictable condition, it was necessary to compare saccade curvatures between the no TMS, rPPC TMS, and M1 TMS conditions within a common window of saccade latency. The lower and upper bounds of this window for each participant were specified as the mean latency of the first bin of the rPPC TMS condition and the last bin of the no TMS condition, respectively. The width of this latency-constrained window was ~70 ms on average across subjects. One participant was excluded (only from this analysis) because it was not possible to define a suitable window. That is, for this participant, saccade latencies of the rPPC TMS condition were prolonged to an extent such that the mean latency of the first bin of rPPC TMS condition was longer than the mean latency of the last bin of no TMS condition. The grand averaged saccade curvature of each TMS condition over the windows when the target was unpredictable, as shown in Fig. 9A. ANOVA still showed a significant main effect of TMS \( F(2,18) = 5.218, P < 0.05 \). Post hoc LSD tests showed that saccade curvatures in these unpredictable windows from the rPPC TMS condition were significantly more away from distractor than both the no TMS condition \( P < 0.001 \) and the M1 TMS condition \( P < 0.05 \). However, in these unpredictable windows, the differences of saccade curvatures between M1 TMS and no TMS conditions were also significant \( P < 0.05 \).

The SOFCT was also applied to these latency-constrained data to clarify the aforementioned possibility in the view of motor control. Figure 9B shows the modeling result in the transverse direction. Both the recovery torque as well as the motor command of the rPPC TMS condition showed a significant window (row 3 of Fig. 9B, \( P < 0.05 \) with FDR control...
that was more negative than the no TMS condition. The differences between the rPPC TMS and M1 TMS conditions were also significant in approximately the same window (P < 0.05, uncorrected) but did not survive under FDR correction. Both of the above tests were consistent with the corresponding tests for saccade curvature. No significant effect was observed in the M1 TMS-no TMS paired t-test, which was not consistent with the findings for saccade curvature, which did show a significant effect. This inconsistency suggested, from the view of motor control, that the influence of M1 TMS on saccade traces was limited. Currently, it is not possible to be clear about the origin of this inconsistency. If saccade traces were indeed significantly affected by M1 TMS, as suggested by the effect on saccade curvature, it was probably due to the fact that some saccade curvature related brain regions (e.g., frontal eye field, rPPC) were indirectly perturbed by M1 TMS to a minor degree. On the contrary, if M1 TMS did not significantly affect saccade traces, as suggested by the results on motor control, this inconsistency might infer that saccade curvature may be indicating an overestimate of the effect from...
M1 TMS. This is also the reason why we suggest using the SOFCT to confirm the effect of TMS on saccade curvature and why we offered an extra control condition (M1 TMS) to ensure the importance of the rPFC in shaping saccade curvature.

These clarifications, both in view of saccade curvature and motor control, suggest that although the preceding analysis revealed a tendency of curvature development over latency in the rPFC TMS condition when the target was unpredictable, there was a pure rPFC TMS effect on saccade traces that was not related to the prolonging saccade latency.

DISCUSSION

The aim of the present study was to investigate the distractor modulation during eye movement in various TMS and target predictability conditions, both in view of saccade curvature and motor control. The analysis of motor control (modeled by the SOFCT) was done along with the analysis of saccade curvature (slope curvature) throughout the entire study to determine the relationship between them. The inference from the model produced four conclusions about the dynamic characteristics of distractor-induced saccade curvature: 1) the dynamic mechanism that caused saccades to curve away from the distractor is the motor command along with the consequential torque in the transverse direction; 2) the transverse torques are composed of a short period of initial torque that causes the saccade to deviate away from the distractor and a relatively longer period of recovery torque that brings the deviated trace back to the target; 3) when the target was unpredictable, rPFC TMS increased the initial torque that deviated the saccade away from the distractor; and 4) the control policy may play the role of curving the deviated saccade back toward the target location.

In the unpredictable condition, rPFC TMS showed the greatest recovery torque that curved the deviated saccade back toward the target location. The main contribution of the modeling results was to quantify the suppression effect of the distractor in the search task and the level of motor control revealed by the motor command and torque. This is also the first TMS study to characterize the modulation of rPFC TMS to this level of detail.

Consequently, the slope curvature may give an index of the effect of the initial torque along with the recovery torque in the transverse direction of a saccade. The correlation analysis in this study revealed that 1) the slope of the first segment of a saccade trace is correlated to the initial torque in the transverse direction and 2) the slope curvature (the slope of the fourth segment minus the slope of the first segment) is correlated to the recovery torque that curved the deviated saccade back toward the target location. Therefore, the definition of slope curvature does not mean that there is nothing of consequence happening during the second and third segments of a saccade trajectory. On the contrary, slope curvature was proved in the present study to be highly correlated with the recovery torque, which, in general, occurs and achieves significance in the second and third segments of a saccade trajectory. Thus, the SOFCT gives the picture that the difference between the slope of the fourth segment and the slope of the first segment is the issue of the recovery torque.

Concerning the mechanism that caused the initial deviation away from the distractor, two hypotheses have been proposed to explain the effect (Doyle and Walker 2001; Walker et al. 2009). The first is the “remapping” hypothesis (Sheliga et al. 1994), which was based on the findings that monkey lateral intraparietal sulcus (LIP) cells have receptive fields corresponding to the postsaccadic position of a stimulus that fire at the start of a saccade (Duhamel et al. 1992). According to the premotor theory, covert attention to a distractor initiates a saccade program to this distractor. When a real saccade is initiated, there also exists a “programmed saccade,” which is performed from the remapped fovea (distractor) to the target. This causes the saccade to deviate away from the distractor. The second is the “suppression” hypothesis, which was based on the idea that the motor response toward a covertly attended distractor should be inhibited before a saccade is made (Sheliga et al. 1995; Van der Stigchel and Theeuwes 2005; for neurophysiological evidence, see McPeek 2006). The suppression hypothesis is an application of the general idea of feedforward control (Basso and Belardinelli 2006). Clarification of which hypothesis is superior is far from the goal of this study. From the results of the present study, the best one may infer according to each one of the two hypotheses is if the remapping model is correct, the rPFC TMS increases the relative weight of the programmed saccade from the distractor to the target, which is unpredictable; if the suppression model is justified, the rPFC TMS causes the brain to oversuppress the distractor when the target is unpredictable. Both hypotheses, together with the SOFCT, infer that there exists greater transverse torques away from the distractor in the initial period of the saccades in the rPFC TMS condition.

Both the remapping hypothesis and suppression hypothesis could only partially predict the initial deviation away from the distractor in a saccade but not account for the possible mechanism why saccades curved back toward the target (Doyle and Walker 2001). The SOFCT used in the present study is a model that involves an internal feedback process that monitors the motor commands and corrects them online. According to this model, the control policy (Eq. 7), which transforms the estimated state of the eye into motor commands, plays the role of correcting the motor commands online to maintain the end point accuracy of the saccade. Therefore, with the aid of this online correction system, the deviated saccade may eventually curve back to the target. It should be noted that the SOFCT used in the present study is compatible with the remapping hypothesis as well as the suppression hypothesis. Through the simple muscle model in Eq. 3, there would be a freedom that allows a solution with initial transverse torques toward the side opposite the distractor, thus rendering the SOFCT compatible with each of the two hypotheses.

It should be noted that when no TMS was applied, we only observed a few trials curving toward the distractor in the predictable condition and did not observe curvature toward the distractor at all in the unpredictable condition. In the present study, we did not observe saccade traces curving toward the distractors, such as those in the global effect (Findlay 1982), where a “target-like” distractor is presented near the target to cause a saccade to curve toward the distractor. The experiment in this study was basically different from those used for exploring the global effect in two aspects. First, in our experiment, the target and distractor locations were programmed not to overlap spatially (distractors in the vertical and horizontal axes but the target in the oblique axis), whereas Findlay (1982) did not impose this restriction in his visual search task. Second, the global effects reported mainly occurred in the setup with
two analogous targets, which may need more brain resources to determine where to make a saccade after the stimulus onset. For the experiment in the present study, this determination was far easier even when the target was unpredictable.

Integrating all of the above discussion, the overall conclusions are as follows. First, some hidden visual selection-related mechanism (remapping, suppression, or other mechanism) was modulated by rPPC TMS such that the relative weight between the target and the distractor was altered. Consequently, the magnitudes of the initial torques away from the distractor in the transverse direction were changed, thus causing the initial deviation away from the distractor. Second, the control policy, which transformed the eye states into motor commands, corrected the deviated saccade trace online to ensure the saccade landed near the target with the magnitudes of these motor commands depending on the degree of initial deviation. The greater recovery torque along with the greater initial torque in the transverse direction caused the saccade trace to curve more away from the distractor in the rPPC TMS condition when the target location was unpredictable.

In this study, the saccade curvature development over saccade latency was almost aligned with the 2011 TMS study by Chao et al. (2011). The only difference, caused by the different definition of saccade curvature, is that when the saccade latency was extremely long (i.e., last bin of the rPPC TMS condition) in the unpredictable condition, the curvature development appeared to be diminished in the present study (Fig. 5). This diminishing was further confirmed by the development of the recovery torque over saccade latency in the rPPC TMS-unpredictable condition (Fig. 8, region bounded by two dashed lines). The most significant increase in saccade curvature occurred in the fourth bin of the rPPC TMS condition and in the fifth bin of the M1 TMS condition when the target was unpredictable. Note that the aforementioned two bins in the two TMS conditions, respectively, are very close to each other in their latencies for most subjects. This reveals that there is perhaps a range of saccade latencies that often appears with the most significant increase in saccade curvature when the target is unpredictable. As shown in Fig. 5, in general, this range represented longer latencies (but not extremely long) and was hard to be achieved without TMS application.

Although the rPPC TMS effect and the bin effect on distractor-induced saccade curvature were present in the unpredictable condition, it is still ambiguous as to whether the curvature increase was caused directly by rPPC TMS or simply accompanied the rPPC TMS-prolonged saccade latency. To resolve this ambiguity, we compared saccade curvatures as well as the motor control estimates between TMS conditions within a subject-specific common window of saccade latency (~70 ms on average across subjects). The results showed a significant rPPC TMS effect both on saccade curvature and motor control (Fig. 9, A and B). This rPPC TMS effect is a pure TMS effect on saccade traces because trials in various TMS conditions shared a common window of saccade latency for each subject. Thus, this analysis in a “latency-constrained window” lessened the association of rPPC TMS effect on saccade curvature with the rPPC TMS-prolonged saccade latency. There was also a significant M1 TMS effect on saccade curvature found in this latency-constrained window analysis, but there was no longer a significant effect on the motor control estimates. There are two possible reasons for this inconsistency: 1) M1 TMS induced a distal effect on one of the saccade-related brain regions (e.g., frontal eye field, rPPC) and the distal effect was too subtle to reach significance in the motor control estimates from SOFCT, or 2) saccade curvature overestimated the effect of M1 TMS. Saccade curvature is merely a representation of the motor control and is less elaborate than the estimates of the SOFCT, although it showed high correlation with the recovery torque estimated by SOFCT in the preceding analysis. Thus, here we are inclined to conclude that the M1 cortex is not directly involved in the function of shaping saccade curvature. It is, at best, only connect to regions involved in the shaping of saccade curvature. Conversely, according to results from this study, the rPPC is more likely to be responsible for the function of shaping saccade curvature, especially when the target is unpredictable.

In summary, these findings have demonstrated that the rPPC is critical in saccade preparation and that the observed TMS effects on saccade curvature are mainly caused by interference in the final stage of saccade preparation. The change of saccade preparation under rPPC TMS interference results not only in the prolongation of saccade latency but also modulates motor control. The motor control of saccades as well as its relation to saccade latency under rPPC TMS interference were revealed by the analysis of both saccade curvature and the motor control estimates in an orienting paradigm that incorporated manipulation of target location predictability and TMS application.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


