TMS over the Left Posterior Parietal Cortex Prolongs Latency of Contralateral Saccades and Convergence

Qing Yang1,2 and Zoï Kapoula1

PURPOSE. This study explored the role of the left posterior parietal cortex (PPC) in saccades, vergence, and combined saccade-vergence movements by means of transcranial magnetic stimulation (TMS) in humans.

METHODS. TMS was applied over the left PPC for 80, 90, or 100 ms after target onset. In a control experiment, TMS was applied over the primary motor cortex at 90 ms after target onset.

RESULTS. Relative to no TMS trials, TMS over the left PPC increased the latency of only certain types of eye movements: saccades to right, convergence, and convergence combined with rightward saccades. It had no such effect on saccades to the left, divergence, saccades combined with divergence, or left saccades combined with convergence. TMS over the vertex had no effect on the latency of any type of eye movement. Thus, the effects of TMS on latency are both area- and eye-movement specific. TMS of the left PPC or the motor cortex did not alter the accuracy of any type of eye movement. The results are in contrast to those of prior studies of the right PPC, which is involved in the initiation of any type of eye movement.

CONCLUSIONS. The findings suggest that the right PPC is involved primarily in the processing of fixation disengagement, whereas the left PPC provides the signal that is also necessary to initiate eye movements and could occur in parallel with the process (model of Findlay and Walker). Such a functional role of the left PPC seems to be topographically organized and concerns a saccade to the right and convergence alone or combined with a saccade to the right. (Invest Ophthalmol Vis Sci. 2004;45:2231–2239) DOI:10.1167/iovs.03-1291

A large cortical network including the posterior parietal cortex (PPC), the frontal eye field (FEF), and the prefrontal eye field (PEF) is involved in the control of eye movements.1,2 The PPC has been extensively studied for its crucial role in triggering of saccades. Electrical stimulation of the monkey PPC triggers saccades.3–5 Lesions in this area result in increasing latency of reflexive visually guided saccades in monkeys and humans.6,7 Functional magnetic resonance imaging (fMRI) shows that this area is highly activated during preparation of visually guided saccades.8 There is some evidence in monkeys, and recently more in humans, that the PPC is involved in the control of vergence eye movements.9–11 Anatomic and neurophysiological studies indicate the existing of functional and structural asymmetries between the two hemispheres in the PPC areas. For example, MRI revealed anatomic asymmetries of the sulcal demarcation of the posterior operculum from the parietal cortex that correlate with handedness in normal subjects.12 Itoh et al.13 found that the left parietal lobe plays a more significant role in cortical processing during a piano performance than the right parietal lobe. Patients with lesions in the right PPC showed significant increases in latency in both directions of reflexive visually guided saccades, whereas patients with lesions in the left PPC showed a significant increase in latency only with saccades made contralaterally to the lesion.7 Muri et al.14,15 using the transcranial magnetic stimulation (TMS) technique, showed hemisphere asymmetry in PPC control of memory-guided saccades and visuospatial attention. They found that TMS over the right PPC increases the percentage of error amplitude contralateral to memory-guided saccades, whereas TMS over the left PPC has no such effect. For smooth pursuit, patients with lesions involving the right PPC had significantly more severe impairments than patients with left-side lesions.16

In previous studies, we found that TMS over the right PPC prolongs the latency of saccades in both directions and also of vergence and combined saccade-vergence eye movements.11 The role of the left PPC in vergence eye movements (pure or combined) is entirely unexplored. Therefore, the main goal of this study was to investigate the effect of TMS over the left PPC on visually guided saccades, vergence, and combined vergence-saccade eye movements. Such a repertoire of eye movements is continuously used to explore the three-dimensional (3-D) environment, to fixate objects located at different distances or directions or both.

METHODS

Subjects

Five healthy adult subjects, three women and two men, participated in the experiment. Their ages ranged from 29 to 46 years (mean 37.0 ± 6.4). All subjects had normal or corrected-to-normal vision. Binocular vision was assessed with the TNO test of stereovision; all individual scores were normal, 60 minutes of arc or better. Each subject gave informed consent to participate in the study. This investigation was approved by the local ethics committee and was consistent with the Declaration of Helsinki.

TMS Localization

A single-pulse TMS was applied by a magnetic stimulator (model 200; Magstim, Whitland, Wales, UK) with a figure-eight coil (each wing, 70 mm in diameter). The left PPC was stimulated by placing the coil 5 cm posteriorly and 3 cm laterally to the vertex. This criterion has been used in prior studies.11,17 The PPC is located in the caudal part of the parietal lobe, including the superior and inferior parietal lobules. Such placement of the coil involved stimulation of the region of the poste-
rior part of the intraparietal sulcus, which appears to play an important role in the control of eye movements. The coil was placed on the scalp with its handle oriented backward and 45° leftward relative to the midline. The left PPC was stimulated at 60% to 80% of total stimulator output, depending on the subject, which was well above motor threshold and did not cause blinks (monitored on recording time). Similar capacity stimulation has been used by others. The time of increase of the pulse was 5 μs, the decay lasted 160 μs, and a click occurred simultaneously with the stimulation discharge. For the main experiments, TMS over the left PPC could occur 80, 90, or 100 ms after the onset of the target. For the control experiment, TMS stimulated the primary motor cortex when the coil was placed on the vertex with the handle oriented backward at 90 ms after target onset. For reference experiments without TMS, the stimulator was switched on but the coil was placed 30 cm over the head of the subject and oriented toward the ceiling.

Visual Display
The visual display consisted of LEDs placed at two isovergence circles: one at 20 cm from the subject and the other at 150 cm. On the close circle three LEDs were used: one at the center and the others at ±20°. The required mean vergence angle for fixing any of these three LEDs was ±1°. On the far circle, five LEDs were placed: one at the center, two at ±10°, and two at ±20°. Fixation on any of these LEDs required vergence angle of 2.3°.

Oculomotor Procedure
In a dark room, the subject was seated in an adapted chair with medical collar. The subject viewed binocularly and faced the 3-D visual display of the LEDs. The visual display of the LEDs was placed at eye level to avoid vertical eye movements. Note that all LEDs were highly visible at all target locations as at every trial (of the calibration or main task, see below) but only one LED light was on at a time.

Calibration Task
The subject made a sequence of saccades to a LED target located 0°, ±10°, and ±20° at the far and then at the near isovergence circle. During each of these trials, the target remained on each location for 2 s (a period sufficiently long to allow accurate and stable fixation). The subject was instructed to fixate the LED as accurately as possible. From these recordings were extracted the calibration factors.

Main Oculomotor Task
To elicit short-latency reflexive eye movements, we used a gap paradigm. Each trial started by lighting a fixation LED at the center of one of the circles (far or close). After a 2.5 s fixation period, the central LED was turned off, and after a gap of 200 ms, a target-LED was turned on for 2 s. When the target-LED was on the center of the other circle, it called for a pure vergence eye movement, along the median plane. When it was at the same circle, it called for a pure saccade, and when it was lateral and on the other circle, the required eye movement was a combined saccade with vergence eye movement. All target LEDs for saccades were at 20°. All targets along the median plane required a change in ocular vergence of 15°. Similarly, combined movements required a saccade of 20° and a vergence of 15°. In each block, the three types of eye movements were interleaved randomly. All subjects performed five blocks of 60 trials with TMS over the left PPC (20 trials at 80, 90, and 100 ms after target presentation), two blocks of 60 trials without TMS (the click was delivered also at 80, 90, or 100 ms after target presentation), and 1 block of 60 trials with TMS over the vertex delivered at 90 ms after target presentation. The order of the blocks (TMS at PPC, without TMS, or TMS at vertex) was pseudorandom, to avoid fatigue effects.

Eye-Movement Recording
Horizontal movements from both eyes were recorded simultaneously (IRIS device; Skalar, Delft, The Netherlands). The head was stabilized by placing the chin on a frontal rest. Eye position signals were low-pass filtered with a cutoff frequency of 200 Hz, digitized with a 12-bit analog-to-digital converter, and each channel was sampled at 500 Hz.

Data Analysis
Calibration factors for each eye were extracted from the saccades recorded in the calibration task. A linear function was used to fit the calibration data. From the two individual calibrated eye position signals, we derived the conjugate (saccade or saccade component) signal from the mean of both eyes and the disconjugate signal (vergence or vergence component) from the difference between two eyes. The onset of a pure saccade or of the saccadic component of the combined movements was defined as the time when eye velocity exceeded 5% of saccadic peak velocity. The offset was taken as the time when eye velocity dropped below 10 deg/s. The onset and the offset of the vergence signals (for pure vergence movement and for the vergence component of the combined movements) were defined as the time point when the eye velocity exceeded or declined below 5 deg/s. These criteria are standard. The placement of the markers by the computer was verified by one of the investigators scrutinizing saccade and vergence components on the screen. From these markers, we measured the latency of eye movements—for example, the difference between target onset and eye movement initiation (Fig. 1, point i). The eye movement amplitude is the difference between the e, marking the end of movement, and the i, marking the start of the movement (Fig. 1). The gain is the ratio of eye movement amplitude-to-target amplitude. Eye movements in the wrong direction, anticipatory movements (latency shorter than 80 ms), and slow movements (latencies longer than 400 ms) or movements contaminated by blinks were rejected. About 10% of trials had to be rejected (individual rates 8%–14%). Anticipations and some blinks were the most frequent causes of rejection.

The individual mean latencies for each type of eye movement under different conditions were calculated for each subject. Individual means were based on from 10 to 12 measures in the reference condition, 9 to 10 during TMS of the right PPC, and 5 to 6 during TMS of vertex. The group mean latency was the mean of individual means. The one-way ANOVA, the homogeneity of variance of individual means was checked, was used to examine the effect of TMS. The subject was the random factor, and the conditions (no TMS, TMS over the left PPC, and TMS over the vertex) were the fixed factor. The least-significant difference (LSD) post hoc test was used for paired comparisons between the any two conditions.

RESULTS
Effect of TMS on the Latency of Eye Movements
Saccades. Figure 2 presents the individual and the group mean latencies of saccades to the right (Fig. 2A) and of saccades to the left (Fig. 2B) together with the standard error. Data are shown for the reference condition (without TMS); for TMS over the left PPC at 80, 90, and 100 ms after target presentation; and for TMS over the vertex. During saccades to right, all five subjects showed latency prolongation relative to the reference condition for the three time windows of TMS of the left PPC. TMS of the vertex showed no consistent effect on the subjects. The ANOVA test applied on these conditions showed significant effect on the latency (F_{4,16} = 9.71, P < 0.01). The latencies increased relative to the reference condition by 23, 17, and 21 ms during TMS over the left PPC at 80, 90, and 100 ms after target presentation, respectively. These differences were all significant (post hoc test, P < 0.01). The latency difference between TMS over the vertex and the reference condition was 5 ms and was not significant (P = 0.52). In contrast, when comparing TMS over the vertex with TMS over the left PPC, both delivered at 90 ms after target onset, there was a significant prolongation of latency for the rightward
saccades for the left PPC stimulation ($P < 0.01$). For saccades to left, the ANOVA showed no significant effect of TMS conditions ($F_{4,16} = 0.59, P = 0.67$).

**Vergence.** Figure 3 presents the individual and the group mean latencies of convergence (Fig. 3A) and divergence (Fig. 3B) together with standard errors, under different conditions. For convergence, latency prolongation relative to the reference condition existed for all five subjects during TMS of the left PPC and for all three time windows. ANOVA showed a significant condition effect on the latency of convergence (no TMS, TMS of the left PPC, and TMS of the vertex, $F_{4,16} = 4.48, P < 0.01$). Relative to the reference condition, group mean latencies of convergence increased by 22, 19, and 31 ms under TMS over the left PPC at 80, 90, and 100 ms, respectively; all these increases were significant (post hoc tests, all significant at $P < 0.05$). The comparison of the latency difference of convergence between TMS over vertex and reference condition was not significant ($P = 0.95$). In contrast, the convergence latency with TMS over the left PPC at 90 ms was significantly longer than that in the condition of TMS over the vertex also delivered at 90 ms after target onset ($P < 0.05$). For divergence, the ANOVA showed no significant effect of TMS conditions ($F_{4,16} = 0.65, P = 0.64$).

**Combined Convergent Eye Movements.** Figure 4 presents the individual and the group mean latencies together with SEs for convergence combined with saccades to the right (Fig. 4A) and for convergence combined with saccades to the left (Fig. 4B). Data are shown for the reference condition; for TMS over the left PPC at 80, 90, and 100 ms after target presentation; and for the condition of TMS over the vertex. During convergence combined with saccades to right, relative to the reference condition, all five subjects showed prolongation of latency for the two components under TMS of the left PPC and for all three time windows. TMS of vertex had no effect. There was significant condition effect on the mean group latency for both saccade and vergence components ($F_{4,16} = 3.71, P < 0.05$ for the saccade component and $F_{4,16} = 3.47, P < 0.05$ for the convergence component). The latency prolongations of group means relative to the reference condition were 27, 21, and 20 ms for the saccade component, and 21, 22, and 20 ms for the convergence component during TMS over the left PPC at 80, 90, and 100 ms after target onset, respectively. All these prolongations were significant (all $P < 0.05$). The latency differences between TMS over the vertex and the reference condition were small for both components of combined movements to right, and they were not significant (both $P > 0.05$). Relative to TMS over the vertex, the latency in the condition of TMS over the left PPC at 90 ms was significant longer for both components of combined convergent movements to right ($P < 0.05$). For combined convergence with saccades to left, there was no significant effect on the group mean latencies for either component under TMS conditions ($F_{4,16} = 1.71, P = 0.19$ for saccade component and $F_{4,16} = 0.51, P = 0.73$ for convergence component).

**Combined Divergent Eye Movements.** Figure 5 presents the individual and the group mean latencies of combined movements to right (Fig. 5A) and for divergence combined with saccades to left (Fig. 5B) under the five different conditions. Individual data showed no consistent pattern of latency changes under TMS conditions. The ANOVA showed no significant effect of TMS conditions on the group mean latencies of divergence combined with saccades to right ($F_{4,16} = 0.36, P = 0.85$ for the saccade component; $F_{4,16} = 0.51, P = 0.73$ for convergence component) or of divergence combined with saccades to left ($F_{4,16} = 1.92, P = 0.16$ for the saccade component; $F_{4,16} = 0.99, P = 0.44$ for the divergence component).

**Effect of TMS on the Accuracy of Eye Movements.** To estimate the accuracy of eye movements, we measured the gain (amplitude of eye movement/amplitude of target; see the Methods section). The group mean values of gain are presented in Figure 6 for pure eye movements (Fig. 6A) and combined saccade–vergence eye movements (Fig. 6B) under the different experimental conditions. The ANOVA applied separately for leftward saccades, rightward saccades, convergence, divergence, components of combined convergent movements and components of combined divergent movements showed no significant TMS effect on the gain of eye movement (all $P > 0.05$).

In summary, the TMS over the left PPC caused latency prolongation relative to the condition without TMS for rightward saccades, convergence, and convergence combined with rightward saccades. TMS over the vertex had no effect during any movements. TMS over the left PPC or over the vertex had no effect on the accuracy of any type of eye movements studied.
DISCUSSION

The main findings of this study are: TMS over the left PPC increases the latency of only certain types of eye movements among the repertoire studied: saccades to right, convergence, and convergence combined with rightward saccades. TMS over the vertex did not increase the latency of any types of eye movements. Thus, the effects of TMS on latency were both area- and eye-movement specific and will be discussed in the following sections.

Increase of Contralateral Saccade Latency

TMS over the left PPC caused a significant latency increase in rightward saccades (i.e., contralateral to the stimulated site). The increase was similar for all three time windows studied (80, 90, and 100 ms after target onset). Our findings are in agreement with the study of patients with lesions of the left PPC by Pierrot-Deseilligny et al. who showed that an increase in latency was significant only during saccades made contralateral to the lesion. More generally, our findings are also in agreement with electrophysiology showing contralateral control of saccades not only for PPC but also for the other areas such as the FEF. More related to the present study is the work of Leff et al. who found that the repetitive TMS over the left PPC slowed reading speeds in the whole array of rightward reading saccades. Such effect was robust, delaying each new reading saccade by 50 ms, irrespective of the position of words in the array. The results suggest the dominance of the left PPC over the right in controlling rightward oculomotor behavior during reading. Our previous study of TMS over the right PPC showed an increase in the latency of saccades in both directions. These findings are again in agreement with the study of patients. Certain specialization of the right hemisphere, and more precisely of the right parietal lobe has been found for certain functions, such as visuospatial function, the control of eye deviation, reflexive visually guided saccades, and memory-guided saccades. The right PPC according to these investigators would be involved in the process of fixation disengagement, which is necessary for any eye movements to occur. Findlay and Walker proposed a model of the brain pathways involved in saccade programming. They presumed that there exists the separation of the pathways controlling the WHEN and the WHERE information for the triggering of saccades. The WHERE stream is a set of interconnected activity maps, resulting in a "salience map," from which the saccadic target location is selected. In contrast, the WHEN stream is envisaged as a single individual signal whose activity level varies. The competitive interaction of the fixate center (WHEN system) and move center (WHERE system) may occur in the different brain centers and determines the initiation of the saccades. Based on this model, the bilateral PPC maybe involved in different neural pathways for controlling saccades.
The left PPC could be more involved in the WHERE pathways and the right PPC in the WHEN pathways, the competitive interaction between the determiners. The limit contralateral action of the left PPC is thus compatible with such a model in which activity of the left PPC when forming a salience map leads to saccade triggering by influencing the balance with the fixation center.

**Prolongation of Convergence Latency**

PPC was also involved in control of vergence eye movements. Physiological studies in animals showed that the neurons of the lateral intraparietal area of the PPC change their activity as a function of both direction and depth of the target. There are reports of patients with lesions in the right or the left PPC who showed poor vergence control. Stein et al. reported poor vergence in children with developmental dyslexia that the investigators attribute to disorder of visuospatial processing functions of the right hemisphere—namely, of the right PPC. The role of the right PPC in the initiation of vergence was first examined by Kapoula et al. It was found that TMS of the right PPC interferes with initiation of both convergence and divergence. The role of the left PPC on initiation of vergence is examined herein for the first time. TMS over the left PPC increased the latency only in convergence but not in divergence, which suggests a space segregation, as convergence involves a shift of the gaze in the close space, whereas divergence involves a fixation from the close to the far space. Neurophysiological and neuropsychological studies have shown that the near and the far space (within and beyond arm’s reach) are coded in different brain areas and by different mechanisms.

The frontal lobe of the monkey has been proposed to be involved in far space representation. Near space, in contrast, seems to be presented in frontal area 6 and in the rostral part of the inferior parietal lobe, area 7b, and area VIP. Bjoertomt et al. showed in humans that transcranial magnetic stimulation of the right PPC or the right ventral occipital lobe selectively induced a significant shift to the right in the perceived midpoint for near and far space, respectively. Weiss et al. measured regional cerebral blood flow with positron emission tomography in normal subjects who performed manual bisection or made line bisection judgments. The investigators found that near space presentation enhanced left occipital-parietal, parietal, and premotor cortex activity, whereas far space presentation enhanced activations in occipital cortex extending into the medial occipitotemporal cortex bilaterally. Taken together, evidence from different studies indicates that the PPC, especially the left PPC, is involved in the control of eyes and hands within near space. Convergence is a type of eye movement allowing the transition from far to near space, and its initiation could be particularly dependent on the left PPC.
In our study, we used three time windows for delivering the TMS over the left PPC: 80, 90, and 100 ms after target onset. One could argue that the absence of a TMS effect on divergence latency may be due to inappropriate TMS delivery (too early or too late). Previous studies suggested that the visual input presented as target in the right hemifield reaches the left primary visual cortex by 40 to 60 ms and then transmitted to the parietal cortex by 80 ms. At 100 ms, the bilateral information is sent to the frontal cortex including the FEF through corticocortical connections. Therefore, the windows of 80 to 100 ms cover the total period during which the subject is susceptible to the effect. Thus, we suggest that the absence of the TMS effect on divergence is due to specification of the left PPC for convergent movements. It is interesting to note, however, that for convergence the time window is not narrow. TMS prolonged convergence latency as well as saccades or combined movements (see the Results section) similarly when delivered at 80, 90, or 100 ms after target onset. This wide window is compatible with the idea that left PPC processing takes a certain amount of time. It is also compatible with the idea of the Findlay and Walker model for progressive building of a salience map in competition with the fixation center rather than a single individual signal, as believed by us for the right PPC.

**Effect on Combined Saccade–Vergence Movements**

In everyday life, pure eye movements—isolated saccades and vergence—are scarce. At near and intermediate distances, most frequently we perform combined saccade–vergence eye movements to fixate objects that differ both in direction and in depth. Such combined saccade–vergence movements are not the simple addition of the saccade and vergence but a complex interaction between two systems. For example, the vergence movement is believed to be facilitated or enhanced when it is combined with saccades in normal adults—for example, vergence velocity is higher during combined movements than during isolated vergence, and reciprocally saccades have been found to be slower when combined with vergence. The interaction of these two systems at the cortical level is less studied. An earlier study suggested the high correlation of latency between saccade and vergence components of combined eye movements. TMS over the right PPC prolonged latency of both components of combined eye movements but did not affect their correlation of latency. These data suggested the high interaction of saccade and vergence even at the cortical level, involving a common decision mechanism for the initiation of the two components. In agreement with the prior TMS study in the present study, TMS of the left PPC affected...
both saccade and convergence components of rightward convergence movements similarly. The correlation of latency between the two components was $r = 0.95$ in the reference condition and $r = 0.93$ in the TMS condition. The fact that the TMS had an effect only during convergence combined with rightward saccades clearly indicates, once more, that decision and triggering mechanisms are functioning in common for the depth and direction location in which the left PPC seems to specialize.

Functional Asymmetry of the PPC and Eye Movement Control in Direction and Depth

Kapoula et al.\textsuperscript{11} showed that TMS over the right PPC causes latency prolongation in both saccade directions, during convergence and divergence, and during combined saccade–convergence eye movements, both divergent and convergent. This indicates an omnidirectional and omnidepth involvement of the right PPC. In contrast, the effects of TMS over the left PPC increases the latency only during contralateral saccades, convergence, and convergence combined with rightward saccades. Taken together, these studies suggest a functional dissociation of the two hemispheres of the PPC for controlling eye movements. As mentioned, the structures, size, and other functions of two hemispheres in many cortical regions are asymmetrical. Iwasaki et al.\textsuperscript{46} found left-to-right differences in cerebral structures of the parietal and temporal region by an anatomic analysis of the medullary branches after a computed tomographic examination. Mottaghy et al.\textsuperscript{47} found that interference by TMS on the verbal working memory occurs earlier, after stimulation of the right than of the left hemisphere. They suggested that left- and right-side brain areas may be involved in parallel in processing of semantic and object features of the stimuli, respectively. Muri et al.\textsuperscript{15} in a TMS study observed that parietal influence on visuospatial attention is mainly controlled by the right lobe. There is also evidence in patients to suggest asymmetrical eye movement control of the PPC, especially in saccades.\textsuperscript{7} Oyachi and Ohtsuka\textsuperscript{48} found that TMS of the right PPC degraded accuracy of both rightward and leftward memory-guided saccades. In contrast, TMS of the left PPC had no effect on the accuracy of eye movements. Our findings on the absence of the effect of TMS in the left PPC on the accuracy of eye movements is in line with the study of Oyachi and Ohtsuka.\textsuperscript{48} Lekwuwa and Barnes\textsuperscript{16} observed that patients with lesions involving the right posterior parietal cortex and/or right dorsolateral frontal cortex had significantly more impairments on smooth pursuit than those with left-side lesions. Perhaps this is the result of relative dominance of the right cortex for visuospatial functions. Another issue to
be considered is the efficacy of TMS, which could depend on the surface configuration of the cortex, which is different between the right and the left hemispheres in humans. Nevertheless, the specificity of the effects we observed in the current study cannot be reconciled with such simple anatomic explanation and TMS efficacy. A last possibility, but less likely, is that different neural circuitries process signals for initiation of different types of eye movements with different time constants. As we explained, the time windows we studied covered all the critical period for eye-movement initiation. Given all these considerations we conclude that this study indicates a functional specificity of the left PPC for the initiation of saccades to right, saccade to right together with convergence, and convergence along the median plane.

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References


