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Human Movement Science 21 (2002) 377–386

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## Eye–hand interactions differ in the human premotor and parietal cortices

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### Abstract

In order to successfully look at and reach for a visual target the central nervous system must perform a complex sensorimotor transformation. How this transformation is mapped onto relevant brain structures has become the subject of much recent investigation. In the present paper we examined the contribution of the human premotor cortex (PMC) to this transformation process during a task requiring coordinated eye and hand movements. For this purpose, we made use of single-pulse transcranial magnetic stimulation (TMS) to temporarily disrupt the processing occurring in the PMC during task performance. Subjects made open-loop pointing movements accompanied by saccades of the same size or two or three times larger. Under normal circumstances without TMS, the pointing movement amplitude increased with saccade amplitude. When TMS was applied over the PMC 100–200 ms after target presentation, the influence of saccade amplitude on the pointing movement amplitude was increased. This is the opposite effect to that observed in a previous study [*Journal of Neurophysiology* 84 (200) 1677–1680] when TMS was applied over the posterior parietal cortex (PPC) during the same task. We suggest that this pattern of results is consistent with the coding of the reach plan in eye-centered coordinates in the PPC and limb-centered coordinates in the PMC.

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*PsycINFO classification:* 2330; 2540

*Keywords:* Saccadic eye movements; Pointing; Premotor cortex; Posterior parietal cortex

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## **1. Introduction**

To successfully look at and reach for an object within extrapersonal space, the location of the object must be converted from eye-centered coordinates to limb-centered coordinates. Non-human primate research has demonstrated that a network of cortical areas, including regions of the parietal and premotor areas, appears to contribute to this transformation. Within the medial portion of the posterior parietal cortex (PPC) there exists a parietal reach region (PRR) which contains arm movement related cells that encode targets with respect to eye position (Batista, Buneo, Snyder, & Andersen, 1999). A large proportion of these reach-selective cells also fire around the time of saccade generation (Snyder, Batista, & Andersen, 2000). The interaction between limb and eye position signals is also apparent in the premotor cortex (PMC). Although reach related cells in the PMC are modulated by eye position (Boussaoud, Jouffrais, & Bremner, 1998; Mushiake, Tanatsugu, & Tanji, 1997), a large proportion of cells in this region explicitly encode the direction and amplitude of limb movement (e.g., Fu, Flament, Coltz, & Ebner, 1995; Riehle & Requin, 1995) and thus provide a signal related to the goal of the reaching response. This limb-centered coding is confirmed by the fact that PMC cells also have visual receptive fields that move with the arm, but not with the eye (Graziano, 1999). It should be noted that this functional dissociation between the preferred frame of reference used within the PPC and PMC is relative rather than absolute. In other words, not all the cells at each site code targets in a specific frame of reference.

Thus, the available evidence from non-human primates suggests that the PPC integrates oculomotor information into the early stages of the reach plan in eye-centered coordinates, whereas the PMC contributes to the preparation of the reach response in limb-centered coordinates based, in part, on contextual information provided by the oculomotor system. We have tested this behaviorally in healthy human subjects by dissociating the metrics of the limb movement from the eye movement. Under such conditions, open-loop pointing responses are influenced by the amplitude of the simultaneously produced saccade (van Donkelaar, 1997) suggesting that the PMC can only partially compensate for the eye-centered reference frame imposed by the PPC. In light of this finding we have more recently starting using transcranial magnetic stimulation (TMS) to gain further insight into how this process maps onto the PMC and PPC. TMS allows one to create a transient virtual functional lesion at a specific time relative to the processing of information related to the task of interest (Pascual-Leone, Bartres-Faz & Keenan, 1999). Of course no actual lesion occurs, rather the magnetic pulse appears to briefly disrupt the pattern of activity in the area being stimulated so that it is unable to contribute in a normal manner to the task being performed. By measuring the resulting changes in performance one can make strong inferences regarding the role played by the area being stimulated. In addition, by manipulating when in time the TMS pulse is delivered relative to different epochs within each trial it becomes possible to address not only if, but also when a specific cortical region is contributing to the task.

Our initial study demonstrated that TMS delivered over the PPC leads to a more complete compensation for the saccadic influence on the reach response (van

Donkelaar, Lee, & Drew, 2000). In the current study, we tested the effects of TMS over the PMC during the task to determine whether the coding of the reaching movement in limb-centered coordinates could also be disrupted. In this way, we were able to gain further insight into the nature of the sensorimotor transformation and how it is mapped onto the human PPC and PMC.

## 2. Methods

Five subjects took part in the experiment (mean age: 25.3). Four of the subjects had also participated in our previous study on the PPC (van Donkelaar et al., 2000). Although this number of subjects is small, the results were consistent enough to obtain significant effects using analyses of variance. Therefore, we felt it was sufficient to test only five subjects to minimize any potential risks associated with TMS. The local ethics committee had approved the experimental procedures and each subject signed an informed consent form prior to the experiment.

The subject was seated in a dimly illuminated room looking at targets projected onto a horizontal mirror. The head was immobilized with a bite bar such that the projected target images were 57 cm from the eyes. Pointing responses were performed on a table positioned underneath the mirror. As shown in Fig. 1, at the beginning of each trial the subject visually fixated a target appearing centrally or  $10^\circ$  or  $20^\circ$  to the left of center. Following a variable delay (500–1500 ms) a second target appeared at the center of the display screen in the midsagittal plane of the subject. At this time the subject was required to align the right index finger with this target without breaking fixation. A small disk on the table facilitated this task. After a further variable delay (500–1500 ms) both targets disappeared and a third target immediately reappeared  $10^\circ$  to the right of center. This served as the cue for the subject to initiate a combined eye and hand movement as quickly and as accurately as possible.

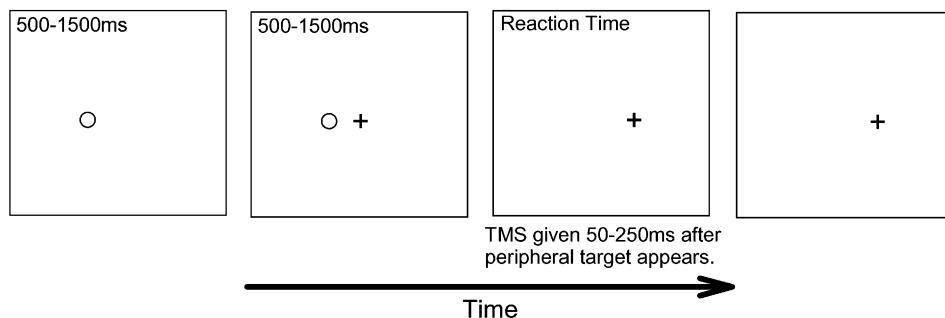


Fig. 1. Sequence of events during a trial with a  $20^\circ$  saccade and  $10^\circ$  hand movement. Initially, the eye target appears (circle), then the hand target (cross). Following a variable delay both targets disappear and a peripheral target appears  $10^\circ$  to the left of center. The subject reacts to this event by looking and pointing at the target. A TMS pulse was given 50–250 ms after the appearance of the peripheral target. Target sizes are not to scale.

Because only a single peripheral target was used it may have been possible for the subject to generate a stereotypical response after a few repetitions, thus relying less on visual guidance. We do not think this was the case, however, because in a previous study (van Donkelaar, 1997) in which two different peripheral targets were used the extent of the effect was very similar to that observed in the present study. Eye movements were measured with an infrared corneal reflection device (Iris Skalar). Pointing responses were measured by recording with a Watsmart system the trajectory of an infrared emitting diode taped to the tip of the right index finger. Both systems were sampled at 200 Hz and calibrated by having the subject look and point to targets at known eccentricities.

A Magstim 200 stimulator was used to deliver single magnetic pulses through a figure-of-eight coil (each wing 70 mm diameter). Coil placement was aided by having the subject wear a tight-fitting swimming cap onto which marks were made. To guard against potential hearing damage, earplugs were worn. The coil was held by hand tangential to the skull with the handle pointing backwards at a 45° angle from the midline. Prior to the experiment the motor threshold for eliciting EMG activity in the right first dorsal interosseous (FDI) muscle was determined by stimulating over the left motor cortex. The threshold was defined as the stimulator output at which FDI activity above 50  $\mu$ V could be elicited on 3 out of 6 trials. Stimulation of the left PMC at 110% of the motor threshold was achieved by moving the stimulating coil 2 cm anterior and 1 cm medial to this motor hot point (Schluter, Rushworth, Passingham & Mills, 1998). The left PPC was localized 7 cm posterior to the motor hot point (Terao et al., 1999). Structural MRIs in one subject with high-intensity signal markers placed at these stimulation sites confirmed these locations (Fig. 2). Subjects did not report any undesirable side effects resulting from the stimulation.

During the task single pulses of TMS were delivered to the left PMC 50, 100, 150, 200, or 250 ms after the appearance of the third target. These trials were randomly

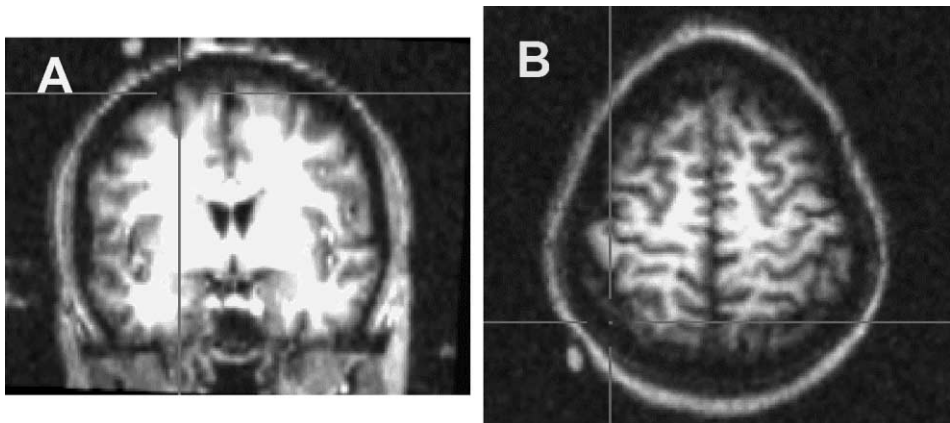


Fig. 2. TMS location sites over the PMC (A) and PPC (B) determined by three-dimensional MRI for a single subject using high-intensity signal markers.

interleaved with trials in which no stimulation occurred. Subjects completed a total of 90 trials composed of the different combinations of saccade and hand amplitudes and TMS delivery times (for a total of five trials per condition). The main dependent variable was the amplitude of the pointing movement in each condition. A compensation index (CI) was computed by obtaining the slope of the line of best fit for the relationship between hand amplitude and saccadic target amplitude and subtracting this value from one. Thus, a CI of zero would indicate that the hand amplitudes were completely determined by the corresponding saccade amplitude, whereas a CI of one would indicate total compensation for the eye-centered frame of reference derived from the PPC. Saccadic amplitudes and the latencies of both pointing and saccadic responses were also measured, although they were found to be unaffected by the stimulation. Analyses of variance were used to test for significant differences across conditions for each measure.

### 3. Results

Fig. 3A shows the group means for hand movement amplitude plotted as a function of saccadic target amplitude. In each condition, as the amplitude of the required saccade was increased so did the amplitude of the reaching movement. This was true when no TMS was delivered over the left PMC as well as when it was given at each of the different delays relative to target appearance. However, when the stimulation occurred at delays of 100–200 ms the slope of this relationship was increased. In other words, the saccade had a larger influence on the reaching response in these conditions than when TMS was not delivered or when it was delivered at the earlier (50 ms) or later (250 ms) delay intervals. If the normal role of the PMC is to compensate for the eye-centered frame of reference imposed by the PPC so that the reach plan can ultimately be carried out in a limb-centered frame of reference, then this result suggests that the compensation occurs during a critical time period. This is clearly captured in Fig. 3B, which displays the CI values for each TMS delivery time over the PMC. The extent of compensation was significantly reduced when processing occurring within the PMC was disrupted 100–200 ms after target presentation. For comparison, the CI values computed from the data in our previous study (van Donkelaar et al., 2000) in which the PPC was stimulated during the same task are also shown. In that study the opposite result was obtained: the extent of compensation was significantly increased rather than reduced. A repeated measures ANOVA revealed a significant two-way interaction between the site and time of stimulation ( $F[4, 30] = 6.98, p = 0.0004$ ). Post-hoc Scheffe's tests revealed that this interaction was due to significant ( $p < 0.05$ ) differences in the CI between the PPC and PMC stimulation sites when TMS was delivered 100, 150, and 200 ms after target presentation.

To determine how these changes in the CI were related to alterations in the actual amplitudes of the limb movements, we transformed the amplitudes into a difference measure relative to the value obtained in the corresponding saccade–hand amplitude combination without TMS. Positive values in this measure indicate that the

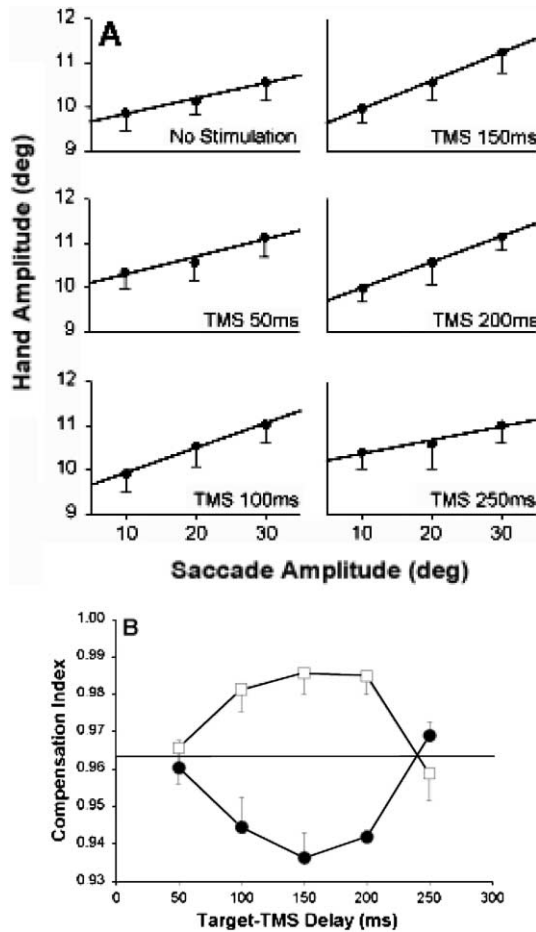


Fig. 3. (A) Group means for hand amplitude plotted as a function of required saccade amplitude during TMS to the left PMC. Condition appears in lower right hand corner of each graph. Error bars, 1 S.E. (B) Group means for the CI plotted as a function of the delay between target presentation and TMS delivery to the left PMC (closed symbols) and to the left PPC (open symbols). Error bars, 1 S.E.

stimulation led to an increase in limb movement amplitude relative to when no TMS was given and negative values the reverse. These values are shown in Fig. 4 as a gray scale contour plot. Fig. 4A demonstrates that the reduction in the CI during PMC stimulation at the 100–200 ms delays was due to a decrease in hand movement amplitudes for responses accompanied by 10° saccades and a increase in hand movement amplitudes for responses accompanied by 20 and 30° saccades. Fig. 4B shows that the increase in the CI during PPC stimulation was due to the opposite pattern of changes in hand movement amplitude. In other words, the changes in CI were due to systematic alterations in the relative amplitudes of the responses.

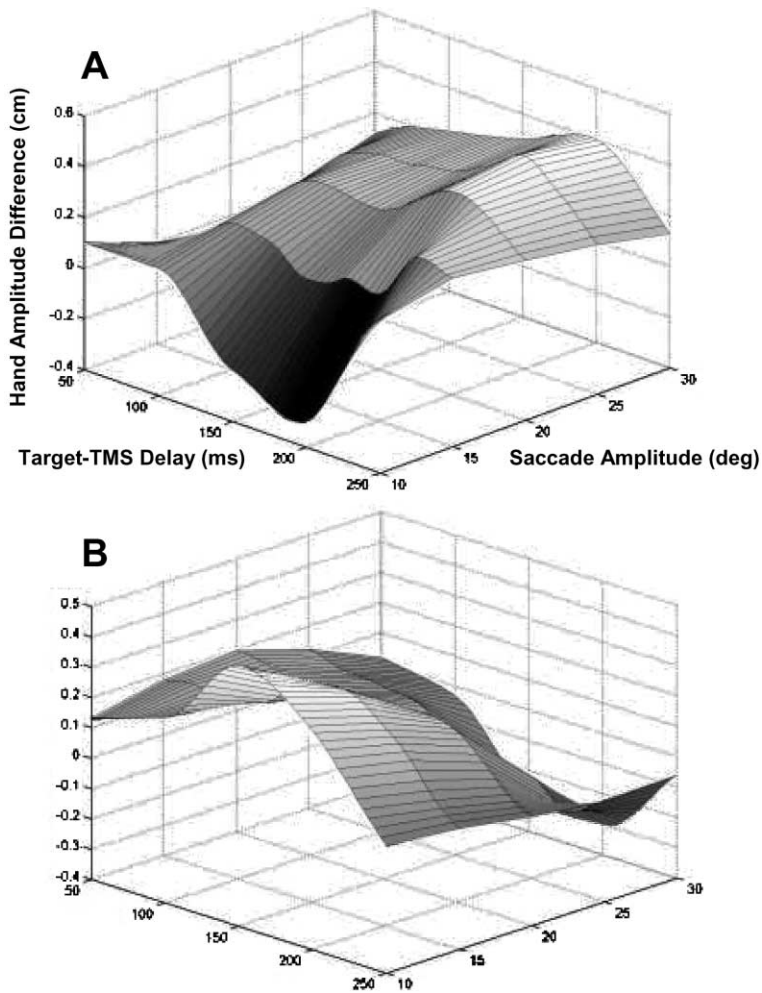


Fig. 4. (A) Gray scale contour plot of hand amplitude difference measure plotted as a function of saccade target amplitude and TMS delay time for PMC stimulation. (B) Same as (A) except for PPC stimulation.

#### 4. Discussion

We have demonstrated that TMS delivered over the PMC leads to an increase in the influence of saccade amplitude signals on the preparation of simultaneously produced reach responses. This change in performance occurred only when TMS was delivered at a critical time period 100–200 ms after target presentation. This strongly implies that normal PMC activation is necessary at this time for normal task performance to occur. In what follows, we discuss how this result contrasts with what we have shown previously in the PPC (van Donkelaar et al., 2000) and what this means

in terms of how the PMC and PPC contribute to coordinated eye and hand movements.

Previous non-human primate single unit recording studies have demonstrated that the PPC contributes to the planning of reaching responses in an eye-centered frame of reference (Batista et al., 1999; Snyder et al., 2000), whereas the PMC is more involved with the preparation of reaching movements in a limb-centered frame of reference (Fu et al., 1995; Graziano, 1999; Riehle & Requin, 1995). Reaching movements, however, ultimately reflect the distance between the hand and the target more so than that between the eye and the target (van Donkelaar, 1997), implying that the limb-centered frame of reference encoded within the PMC compensates for the eye-centered frame of reference occurring within the PPC. Disrupting the pattern of activation in the PMC and PPC with TMS provides an opportunity to examine how these two areas interact during eye–hand coordination tasks. TMS over the PMC led to a decrease in the amount of compensation that occurred: limb movements were now more influenced by the saccade amplitude signal than normal. In contrast, TMS over the PPC led to more compensation than normal. In other words, TMS disturbed the balance of influence each area had on the task. The fact that TMS over the PMC allowed the eye-centered frame of reference arising from the PPC to be expressed more completely suggests that this information must partially travel along more than one route from the PPC to the motor cortex. Neuroanatomical studies have shown that the PPC projects to both the ventral (Luppino, Murata, Govoni, & Matelli, 1999) and dorsal (Johnson, Ferraina, Bianchi, & Caminiti, 1996) portions of the premotor cortex. Because it is unlikely that we were disrupting *all* of the PMC with the TMS pulses, it is possible that the contribution of the portion left unstimulated was responsible for observed behavioral results.

The alterations that were observed in the limb movement compensation at the different stimulation times and sites were due to systematic changes in relative hand movement amplitudes (Fig. 3). The changes in the responses accompanied by 20° and 30° saccades are fairly straightforward to explain. We are claiming that when the PMC was stimulated the eye-centered frame of reference arising from the PPC had a bigger influence on the responses. Thus, oculomotor signals associated with the larger saccades led to significantly larger hand movement amplitudes. When the PPC was stimulated these oculomotor signals were disrupted and the limb-centered frame of reference within the PMC had a bigger influence on the responses. As a result, the hand movement amplitudes became smaller and more appropriate for the pointing distance. This logic can also be used to explain the increase in hand movement amplitude for pointing responses accompanied by 10° saccades following PPC stimulation. Because the hand normally (i.e., when no TMS was given) under-shot the target under these circumstances, this increase again made the responses more appropriate for the pointing distance. Unfortunately, this logic fails to explain the decrease in hand movement amplitude that was observed for pointing responses accompanied by 10° saccades following PMC stimulation. If according to our logic, this stimulation increased the influence of the eye-centered frame of reference arising from the PPC, then it should have resulted in an *increase* not a decrease in the hand movement amplitude. One possible explanation of this paradoxical observation is

that the oculomotor signal that influences the limb motor system may be a damped representation of the actual saccadic output. This has certainly been suggested previously in the context of oculomotor localization tasks (Dassonville, Schlag, & Schlag-Rey, 1992).

Finally, we have stimulated a circumscribed region of cortical tissue in both the PMC and PPC. Thus, it is very likely that we would have obtained different results had we stimulated at different sites within each area. For example, Rushworth, Ellison and Walsh (2001) have demonstrated recently that within the parietal lobe, changing the stimulation site from the supramarginal gyrus to the angular gyrus can differentially disrupt motor attention versus orienting attention, respectively. Given that different parts of both the PMC and PPC have been shown in neurophysiological studies to carry different forms of visual-, eye-, and limb-movement related activity, it would not be surprising to observe different effects of TMS at different portions of each of these cortical areas. Such questions await further research. Taken together, the results from the present study demonstrate for the first time in humans that the PPC and PMC make different contributions to the coordination of eye and hand movements during reaching responses to targets in extrapersonal space.

### Acknowledgements

The authors thank Harold Bekkering and Bas Neggers for organizing the symposium at which this work was presented. The comments of two anonymous reviewers were also helpful in improving a previous version of this paper. This work was supported in part by the National Science Foundation.

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