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Transcranial Magnetic Stimulation Disrupts Eye-Hand Interactions in the Posterior Parietal Cortex

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van Donkelaar, Paul, Ji-Hang Lee, and Anthony S. Drew. Transcranial magnetic stimulation disrupts eye-hand interactions in the posterior parietal cortex. *J Neurophysiol* 84: 1677–1680, 2000. Recent neurophysiological studies have started to shed some light on the cortical areas that contribute to eye-hand coordination. In the present study we investigated the role of the posterior parietal cortex (PPC) in this process in normal, healthy subjects. This was accomplished by delivering single pulses of transcranial magnetic stimulation (TMS) over the PPC to transiently disrupt the putative contribution of this area to the processing of information related to eye-hand coordination. Subjects made open-loop pointing movements accompanied by saccades of the same required amplitude or by saccades that were substantially larger. Without TMS the hand movement amplitude was influenced by the amplitude of the corresponding saccade; hand movements accompanied by larger saccades were larger than those accompanied by smaller saccades. When TMS was applied over the left PPC just prior to the onset of the saccade, a marked reduction in the saccadic influence on manual motor output was observed. TMS delivered at earlier or later periods during the response had no effect. Taken together, these data suggest that the PPC integrates signals related to saccade amplitude with limb movement information just prior to the onset of the saccade.

INTRODUCTION

Despite the fact that behavioral experiments have demonstrated the eye and hand motor systems interact during coordinated responses (Desmurget et al. 1998), how and where these interactions take place within the human brain is poorly understood. Several lines of evidence suggest that a network of parietal and premotor areas play a significant role in this process. Single-unit recording studies in primates (Batista et al. 1999; Boussaoud et al. 1998; Joffrais and Boussaoud 1999; Mushiake et al. 1997; Snyder et al. 2000) and functional imaging studies in humans (Baker et al. 1999) have demonstrated that cells at several sites within this network possess limb movement-related activity that is modulated by eye position. Although these results clearly demonstrate a relationship between the coding of limb movement and static eye position, the nature of this interaction within the human brain during dynamic eye and hand movement responses has not been investigated.

There is behavioral evidence to suggest that signals related to saccadic amplitude influence manual pointing movements:

when an open-loop pointing response is accompanied by a large saccade, its amplitude is greater than when it is accompanied by a smaller saccade (van Donkelaar 1997). This result is consistent with the idea that information related to saccade amplitude is integrated into limb movement signals at one or more sites within the brain. The present study was undertaken to gain a better understanding of how and when such signals interact within the posterior parietal cortex (PPC). This was accomplished by delivering single pulses of transcranial magnetic stimulation (TMS) to transiently disrupt (Pascual-Leone et al. 1999) the activity in the PPC during coordinated eye and hand movements. It was predicted that if the PPC is contributing to the coordination between these two motor systems, then TMS delivered at the appropriate time should cause a significant reduction in the degree of coordination that is observed.

METHODS

Five males (mean age: 28.3 yr) including the authors served as subjects after giving informed consent. Each subject was free from neurological impairments affecting ocular or manual control and had normal or corrected to normal vision. The local ethics committee had approved the experimental procedures. Although the authors were not naïve to the task, any potential to cognitively bias performance was controlled by varying target locations and TMS pulse times in a pseudorandom order across trials. Indeed, the results from the authors were indistinguishable from those from the two naïve subjects.

The subject was seated in a dimly illuminated room looking down at a horizontally oriented mirror onto which target images were projected. Pointing movements were performed open loop with the hand and arm on a table positioned underneath the mirror. The position of an infrared marker on the tip of the right index finger was tracked by a Watsmart system. Eye movements were recorded with an infrared corneal reflection device (Iris Skalar). Both systems were sampled at 200 Hz. The eye movement recording device was calibrated by having the subject fixate targets at known eccentricities prior to data collection. A bite bar was used to stabilize the head.

Single magnetic pulses were generated with a Magstim 200 stimulator and delivered through a figure-of-eight coil (each wing 70 mm diam). The subject wore a swimming cap on which marks were made to aid in coil placement. In addition, earplugs were used to guard against potential hearing damage. The coil was held by hand tangential to the skull, with the handle pointing backward at a 45° angle from the midline. The motor threshold for eliciting electromyographic

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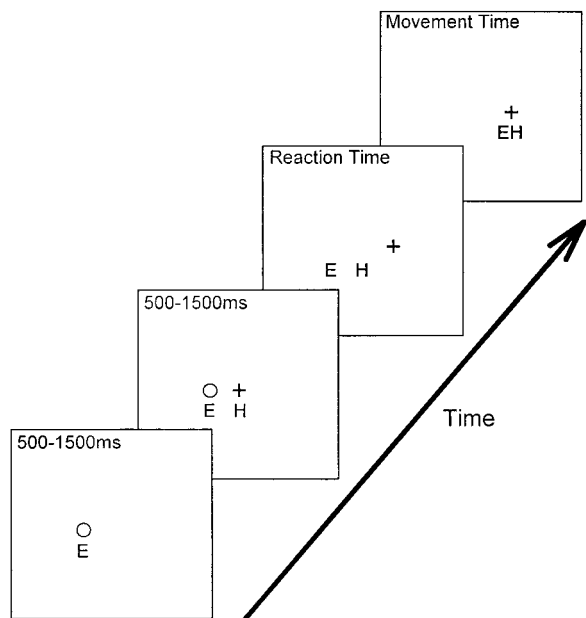


FIG. 1. Sequence of events during a trial requiring a 20° saccade and 10° hand movement. The eye target appears 1st (○), followed by the hand target (+). After a variable delay, both targets disappear, and a 3rd target is presented 10° to the left of center. The subject responds by looking and pointing at this target. E and H represent the position of the eye and hand, respectively, during the trial. Target sizes are not to scale.

(EMG) activity in the right first dorsal interosseous (FDI) was first determined by stimulating over the left motor cortex. The threshold was defined as the magnitude of stimulator output at which EMG activity from the FDI was above 50 μV for at least 3 of 6 trials. Stimulation of the left PPC at 110% of the motor threshold was accomplished by moving the coil to a position 7 cm posterior from this motor "hot point" (Terao et al. 1998). In addition, in a separate session, TMS was applied over the left occipital cortex [2 cm to the left and above theinion (Kamitani and Shimojo 1999)] during the task to control for the nonspecific effects of stimulation. None of the subjects reported experiencing any undesirable side effects as a result of the stimulation.

At the start of each trial a target (0.5° circle) appeared either at the center of the display or 10 or 20° to the left of center. The subject was required to visually fixate this target. After a variable delay (500–

1,500 ms) a second target (0.5° cross) appeared at the center of the display. The subject was required to align their right index finger with this target on the table below the mirror while maintaining visual fixation. A circular disk (1 cm diam) located on the table coincided with the visual position of the target and helped the subject align their finger quickly and accurately. After another variable delay (500–1,500 ms) the first two targets disappeared, and a third target reappeared 10° to the right of center. The subject was required to respond to this event by looking and pointing to the new target position. Thus on some trials the required eye and hand movements had the same amplitude, whereas on others the required eye movement was 10 or 20° larger than the hand movement. Figure 1 shows a schematic representation of the events as they would occur in a trial in which a 20° eye movement and a 10° hand movement were required.

Single pulses of TMS were applied 50, 100, 150, 200, or 250 ms after the appearance of the third target. Each session was comprised of randomly interleaved trials with the three different combinations of saccade amplitude and hand amplitude and the five different stimulation times as well as controls without stimulation. Five repetitions of each trial type were completed resulting in a total of 90 trials.

The dependent variables included the saccadic and pointing movement latencies and amplitudes. The onset and offset of the movements were determined using velocity-time thresholds for each type of response. Latency was defined as the period from the appearance of the third target to the onset of the movement. Amplitude was defined as the difference between the position of the eye or limb at movement onset compared to offset. In most cases, these variables were normalized with respect to the mean of baseline control trials without stimulation. Analyses of variance were used to test whether significant differences existed between stimulation times for each measured variable.

RESULTS

Figure 2, A–C, displays typical eye and hand responses from a single subject performing the task without stimulation. In agreement with our previous findings (van Donkelaar 1997), as required saccade amplitude increased so too did the amplitude of the pointing response. Figure 2D shows the means for hand movement amplitude for this subject plotted as a function of the required saccade amplitude. A linear regression analysis revealed a significant positive correlation ($R^2 = 0.68$) with a slope of 0.0635. It should be noted that subjects quite often undershot the targets for saccades beyond 20°. However,

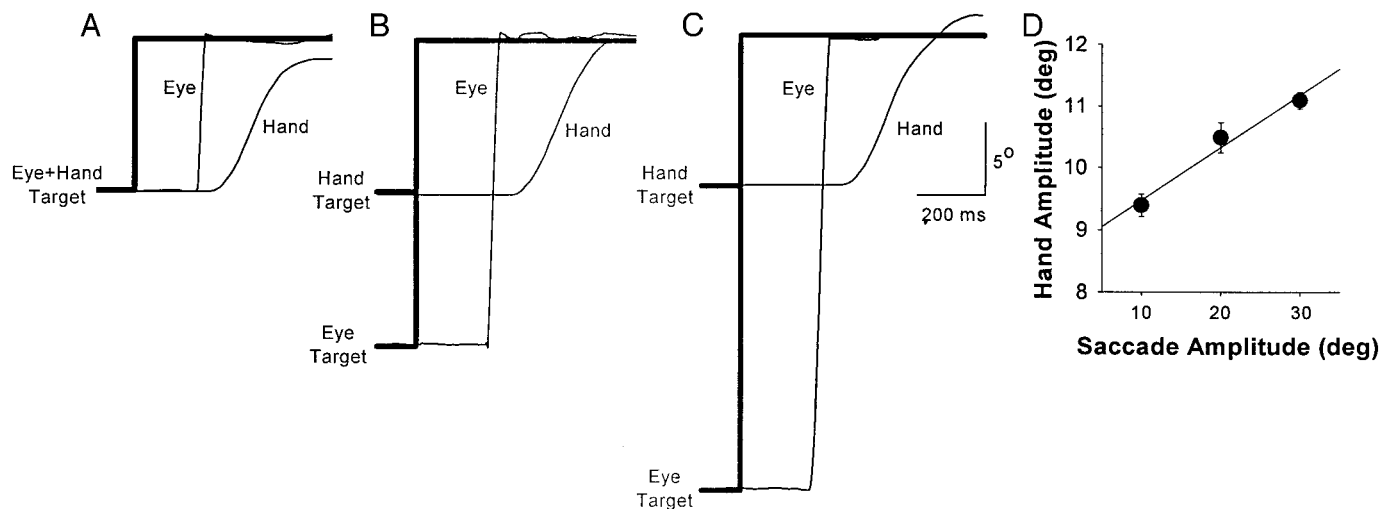


FIG. 2. Typical eye and hand movements from a single subject during responses requiring a 10° (A), 20° (B), or 30° (C) saccade. D: mean hand amplitudes plotted as a function of required saccade amplitude for this subject. Error bars, 1 SE.

to compute our slopes we used the saccade amplitude that was *required* to foveate the target rather than the saccade amplitude that was *actually* produced.

Figure 3A shows the group means for hand movement amplitude for this condition as well as for the conditions in which TMS was delivered to the left PPC. Clearly, the slope was modulated when TMS was applied 100–200 ms after target appearance. Figure 3B displays the slope plotted as a function of the delay between the presentation of the target and delivery of TMS to the left PPC. The data from the control experiment with stimulation to the left occipital cortex are also included for comparison. In this figure the slopes have been normalized with respect to the baseline condition without stimulation. A two-way ANOVA with stimulation site and time as factors revealed a significant interaction between these two variables ($F[4,40] = 5.56, P = 0.0011$). Post hoc Tukey's tests demonstrated that this was due to the slope values being significantly smaller for PPC stimulation at intermediate times compared to earlier or later times or to occipital stimulation at any time. Further analysis revealed no significant changes for hand movement latency, saccadic latency, or saccadic amplitude.

To better understand how the changes in slope following stimulation of the left PPC were related to the initiation of the saccade, the data are replotted in Fig. 3C as a function of the "TMS-saccade onset delay." To obtain this value the time of TMS pulse application relative to the average saccade onset was calculated for each stimulation time and each subject. It is clear that pulses applied 0–100 ms prior to the onset of the saccade caused a substantial reduction in the slope. By contrast, pulses applied earlier or later had much less of an effect.

DISCUSSION

We have shown that transiently disrupting the pattern of activation in the PPC 0–100 ms prior to the onset of a saccade causes a significant reduction in the effect the saccade has on a simultaneously produced limb movement. This occurred despite the fact that the saccade itself remained unaffected (see also Terao et al. 1998). We suggest that this was due to a disruption in the integration of saccade information into the planning of the reach response within the PPC at this time. Stimulation at earlier or later times had no influence, demonstrating that the PPC contributes to these effects during a finite period of time just prior to the saccade. Because the effects were observed during the presaccadic period, the signals must be part of an oculomotor efference copy rather than proprioceptive in origin. Similar inferences have been made previously by Duhamel and colleagues concerning the updating of the representation of visual space in the PPC across saccades (Duhamel et al. 1992a,b). An alternative explanation for the effects we observed is that TMS over the PPC disrupts the ability to effectively distribute attention. This, however, appears unlikely because it should have resulted in systematic changes in reaction time or endpoint variability for both saccadic and pointing responses. It is also possible that the effects we observed were due to disruption of activity within white matter connections passing under or nearby the PPC. If this were the case it would be difficult to establish a causal role between the targeted brain area and performance of the task being tested. Until the appropriate neurophysiological studies can be performed in primates, this concern cannot be defini-

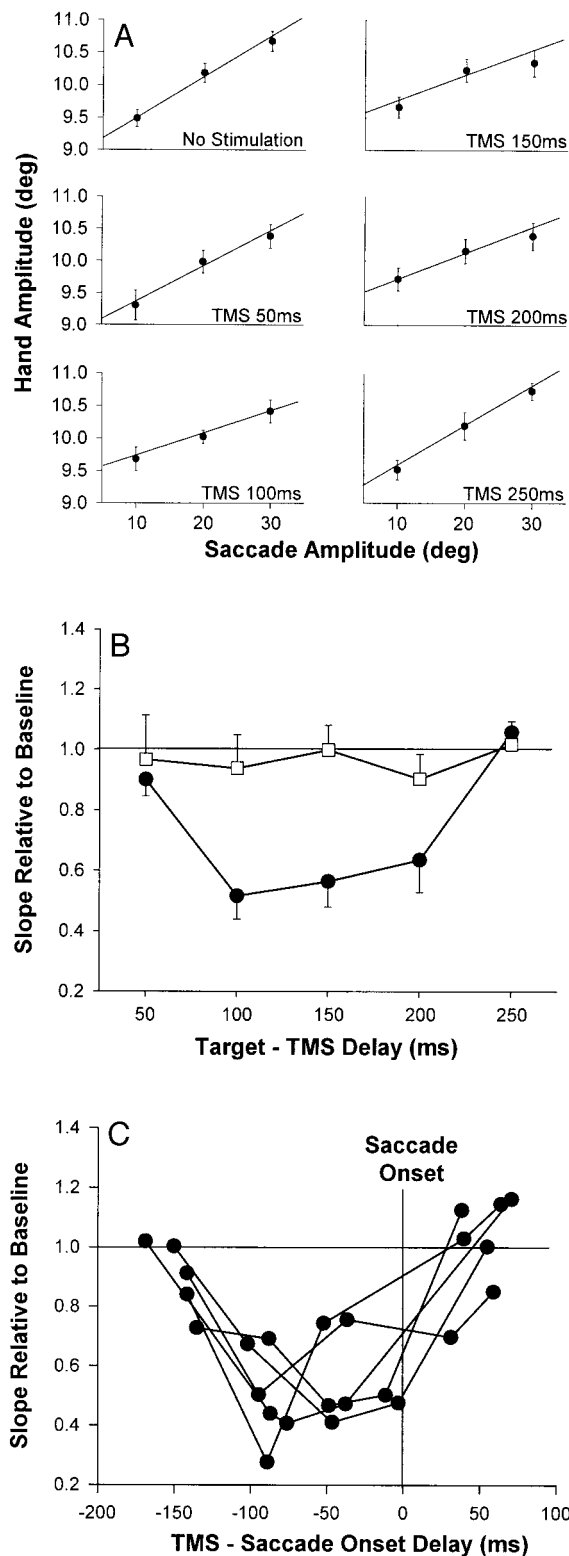


FIG. 3. A: group means for hand amplitude plotted as a function of required saccade amplitude during transcranial magnetic stimulation (TMS) to the left posterior parietal cortex (PPC). Condition appears in *bottom right* of each graph. Error bars, 1 SE. B: group means for slope relative to baseline trials without stimulation plotted as a function of the delay between target presentation and TMS delivery to the left PPC (●) and, as a control, to the left occipital cortex (□). Error bars, 1 SE. C: individual slope values during TMS to the PPC plotted as a function of average TMS-saccade onset delay for each stimulation time.

tively addressed. However, recent studies have provided converging evidence that TMS delivered to brain regions activated during the performance of specific tasks result in behavioral deficits in those tasks (e.g. premotor cortex: Schluter et al. 1999; Toni et al. 1999; visual cortex: Kosslyn et al. 1999).

Desmurget and coworkers (1999) have recently shown that TMS delivered over a nearby region of the PPC (~2.5 cm anterior) disrupts the ability to make corrections to pointing movements in response to unexpected displacements of a visual target. They stimulated at the beginning of hand movement, whereas in the present study the largest effects were observed for stimulation delivered just prior to saccade onset. As such, these two studies suggest that the contribution of the PPC to eye-hand coordination evolves as the response unfolds. In particular, just prior to the onset of an eye movement toward the peripheral target, the PPC integrates information related to saccade metrics into the planning of the subsequent reaching response. After the saccade has ended and the reach has been initiated, the PPC compares target location information with an estimate of current hand position to allow any necessary updating to the ongoing trajectory. Although these functions may appear disparate, both are consistent with the recent proposal that the PPC serves to maintain and update an internal estimate of the world and one's own body (Wolpert et al. 1998). This updating process is required if a saccade is made prior to either a pointing response (present study) or a second saccade (Duhamel et al. 1992a). It is also necessary when the target for a pointing response switches location during the middle of the movement (Desmurget et al. 1999). TMS appears to disrupt the updating process, resulting in deficits that are specific to the function being performed by the PPC at the time of stimulation.

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