Transcranial Magnetic Stimulation of the Prefrontal Cortex Delays Contralateral Endogenous Saccades

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Abstract

■ The contributions of the superior prefrontal cortex (SPFC) and the superior parietal lobule (SPL) in generating voluntary endogenous and reflexive visually guided saccades were investigated using transcranial magnetic stimulation (TMS). Subjects made choice saccades to the left or right visual field in response to a central arrowhead (endogenous go signal) or a peripheral asterisk (exogenous go signal) that were presented along with a single TMS pulse at varying temporal intervals. TMS over the SPFC increased latencies for saccades made in response to an endogenous go signal toward the contralateral hemifield. No effects were observed when the go signal was exogenous and TMS was over the SPFC or when TMS was over the SPL for either saccade type. The delayed contralateral endogenous saccades observed in this study are likely a consequence of disruption in the normal operations of the human frontal eye field. ■

INTRODUCTION

In everyday life, we constantly make eye movements to a number of competing stimuli in the environment. These eye movements are often reflexively driven to foveate objects, such as when attention is captured by a sudden motion or noise that is sensed in the periphery. At other times, the eye movement system is under volitional control, and saccades are made in the service of current task demands. The roles of the superior prefrontal cortex (SPFC), including the frontal eye field (FEF), and of the superior parietal lobule (SPL) in generating these two types of saccades were investigated using single pulse transcranial magnetic stimulation (TMS). Since the SPFC and the SPL have both been associated with eye movements and attention (Andersen, Brotchie, & Mazzoni, 1992; Bruce & Goldberg, 1985; Corbetta, Miezin, Shulman, & Petersen, 1993; Forbes & Klein, 1996; Fox, Fox, Raichle, & Burde, 1985; Pierrot-Deseilligny, Rivaud, Gaymard, Muri, & Vermersch, 1995; Posner, Walker, Friedrich, & Rafal, 1984), these areas were candidate structures for the current investigation.

TMS of the human cortex can transiently impair visual perception when stimulation is over the occipital lobe (Amassian et al., 1989; Beckers & Homberg, 1991) and can also produce twitches in the contralateral hand when stimulating over the hand area of motor cortex. Previous attempts to induce saccadic eye movements with single pulse TMS, however, have been unsuccessful (Muri, Hess, & Meienberg, 1991; Wessel & Kompf, 1991). Rather than inducing saccades, it has been shown that TMS of certain cortical areas can delay visually guided saccades (Priori, Bertolasi, Rothwell, Day, & Marsden, 1993) as well as antisaccades made away from a visual target (Muri et al., 1991). Furthermore, TMS of the posterior parietal cortex (Oyachi & Ohtsuka, 1995) and the supplementary motor area (Muri, Rivaud, Vermersch, Leger, & Pierrot-Deseilligny, 1995; Muri, Rosler, & Hess, 1994) have been associated with the disruption in the accuracy of memory-guided saccades. Because the antisaccade paradigm involves both the suppression of a reflexive visually guided saccade as well as the execution of a voluntary saccade in the opposite direction, and the memory-guided saccade paradigm involves a memory component in addition to the voluntary saccade, the mechanisms that underlie the influence of TMS of different cortical areas on voluntary saccades is uncertain.

The current investigation recorded saccade latencies made to the visual field contralateral or ipsilateral to the TMS. It has recently been demonstrated that chronic

unilateral lesions of the human FEF result in increased latencies of voluntarily generated saccades toward the contralesional field (Henik, Rafal, & Rhodes, 1994). Furthermore, that study showed that latencies of reflexive visually guided saccades toward the ipsilesional field were abnormally inflated. In the present study, two saccade tasks similar to those employed in the study by Henik et al. were used with TMS over the SPFC and the SPL. In one task, a reflexive visually guided saccade was made to a peripheral visual signal. In the voluntary endogenous saccade task, saccades were generated in response to a centrally presented arrowhead.

RESULTS

For each subject in each condition, we computed a median saccade latency for all correct responses. In addition to the trials defined as errors (see "Methods"), saccades that were slower than 750 msec were also excluded from the analysis. Since all error trials were repeated except for those trials with saccade latencies between 750 and 1500 msec, only 0.9% of the trials were left out of the analyses due to errors. None of the error trials were analyzed since a considerable proportion of these errors were due to nonsystematic effects including accidental movement of the eye monitoring spectacles and occasional blinks.

Baseline

The results from the baseline conditions were analyzed first in order to determine whether there was an inherent bias in the subjects to saccade faster to one field. The data from the endogenous and exogenous baseline tasks were each subjected to a t test with the field of saccade (left versus right) as the independent variable.

For saccades made to endogenous signals, there was no difference between saccades made to the left hemifield (303 msec) and saccades made to the right (310 msec) [$t(9) = 1.128$, *ns*]. For saccades made in response to exogenous signals, there was a nonsignificant trend for latencies to be faster toward the right hemifield (256 msec for leftward saccades and 236 msec for rightward saccades) [$t(9) = 1.838, p = 0.097$]. Since neither endogenous nor exogenous saccade latencies were significantly faster toward one visual field, the data were collapsed across fields for each go signal type and are represented by the dashed lines in Figures 1 and 2.

TMS of the Superior Prefrontal Cortex

The mean of the median saccade latencies for endogenous and exogenous go signals while TMS was over the SPFC are presented in Tables 1 and 2, respectively. A separate ANOVA was performed on each of the two go signal types. Both analyses had field of target (contralateral or ipsilateral to the TMS) and TMS pulse to go signal

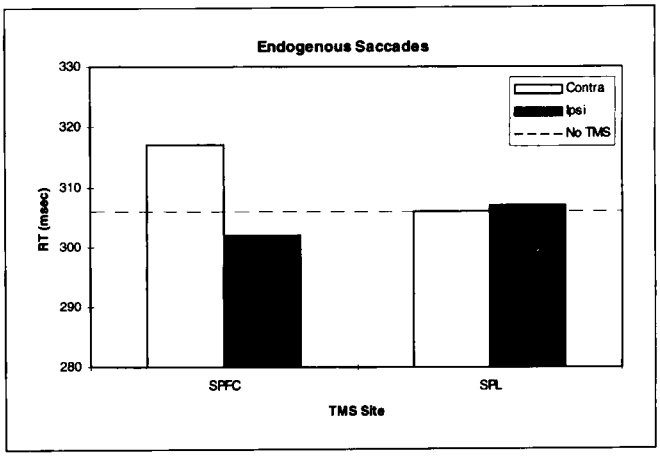

Figure 1. The mean of the median saccade latencies for endogenous saccade conditions. The dashed line represents saccades made in response to a centrally presented arrowhead when there was no TMS. Saccade latencies for subjects that were stimulated over the SPFC are shown in the left half of the figure and saccade latencies for subjects stimulated over the SPL are shown in the right half.

stimulus onset asychronies, or SOA, (−100, 0 , or 100) as the two within-subject factors.[1]

As shown in the left half of Figure 1, saccades made in response to an endogenous signal toward the contralateral field were slower than saccades made toward the ipsilateral field [$F(1,9) = 9.896, p < 0.02$]. There was also a main effect of SOA that was due to increased latencies at the longer SOA intervals [$F(2, 18) = 28.570$, $p < 0.001$]. This effect was present in every TMS condition (see Tables 1 and 2) and is likely due to some nonspecific alerting of a warning signal (Posner & Boies, 1971). The field by SOA interaction was not significant [$F(2, 18) = 1.011$, *ns*].

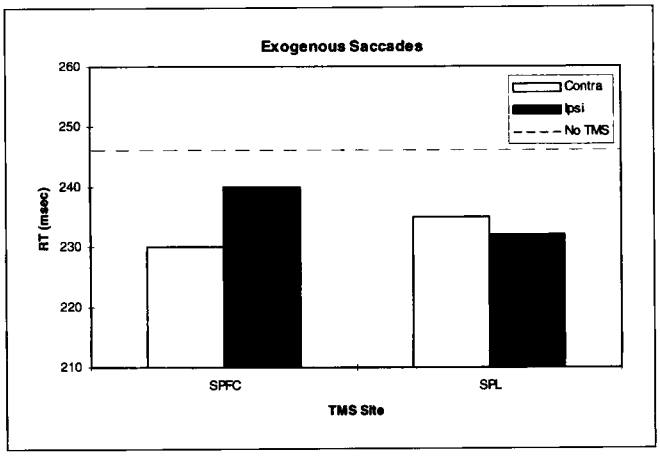

Figure 2. The mean of the median saccade latencies for exogenous saccade conditions. The dashed line represents saccades made in response to a peripheral visual signal when there was no TMS. Saccade latencies for subjects that were stimulated over the SPFC are shown in the left half of the figure and saccade latencies for subjects stimulated over the SPL are shown in the right half.

Table 1. Endogenous Saccade Latencies (*S.D.* in Parentheses)

	Left Hemisphere TMS				*Right Hemisphere TMS*		
TMS Site	*−100*	*0*	*100*		*−100*	*0*	*100*
SPFC	292 (48.4)	301 (30.4)	349 (42.9)	Contra	298 (20.9)	308 (18.1)	353 (33.1)
	274 (36.1)	299 (26.1)	341 (42.6)	Ipsi	271 (25.1)	292 24.3)	335 (35.1)
SPL	281 (59.8)	289 (44.4)	333 (49.2)	Contra	286 (34.9)	309 (42.6)	339 (49.9)
	284 (48.0)	296 (39.2)	333 (69.9)	Ipsi	290 (23.4)	301 (36.4)	337 (35.4)

For saccade latencies in the exogenous task (see Table 2 and Figure 2), there was a significant effect of SOA, again due to longer saccade latencies at the longer SOAs [$F(2, 18) = 16.995, p < 0.001$]. There was a trend for the latencies of ipsilateral exogenous saccades to be slower than those made toward the contralateral field. This trend was in the same direction as that observed in patients with FEF lesions (Henik et al., 1994). In the current study, however, this trend did not approach statistical reliability [$F(1, 9) = 1.057$, *ns*]. The field of saccade by SOA interaction was also not significant [$F < 1$].

TMS of the Superior Parietal Lobule

For saccades made to both endogenous and exogenous go signals while TMS was over the SPL, the only effects that were reliable were the main effects of SOA for both saccade types ([$F(2, 18) = 33.426, p < 0.001$] for the endogenous task and [$F(2, 18) = 80.560, p < 0.001$] for the exogenous task). No other main effects or interactions approached significance (see Tables 1 and 2 and right halves of Figures 1 and 2).

DISCUSSION

The main result of the current study is that TMS of the SPFC increases the latencies of voluntary saccades made toward the visual field contralateral to the side of the TMS. This result is consistent with our previous work done in patients with chronic, unilateral lesions of the FEF (Henik et al., 1994). Since the TMS coil that was used covered a large cortical surface area (see Figure 3), it is likely that this delay of saccades was also due to disruption of the area of the SPFC that includes the FEF. The human FEF as localized through PET studies has been associated with the area at the posterior bank of the middle frontal gyrus, just anterior to the precentral sulcus (Anderson et al., 1994; Fox et al., 1985). As shown in Figure 3, the magnetic field used in this study extended into this area. The current study, however, was not designed to localize the exact anatomical location of the

Table 2. Exogenous Saccade Latencies (*S.D.* in Parentheses)

	Left Hemisphere TMS				*Right Hemisphere TMS*		
TMS Site	*−100*	*0*	*100*		*−100*	*0*	*100*
SPFC	201 (58.6)	185 (45.6)	228 (47.5)	Contra	200 (29.2)	260 (56.7)	305 (76.1)
	218 (43.6)	219 (43.8)	273 (52.0)	Ipsi	201 (28.2)	238 69.7)	292 (69.3)
SPL	182 (24.8)	188 (32.4)	242 (20.1)	Contra	228 (69.8)	260 (76.0)	311 (83.2)
	188 (29.8)	204 (29.7)	259 (32.6)	Ipsi	229 (78.2)	247 (83.0)	268 (101.8)

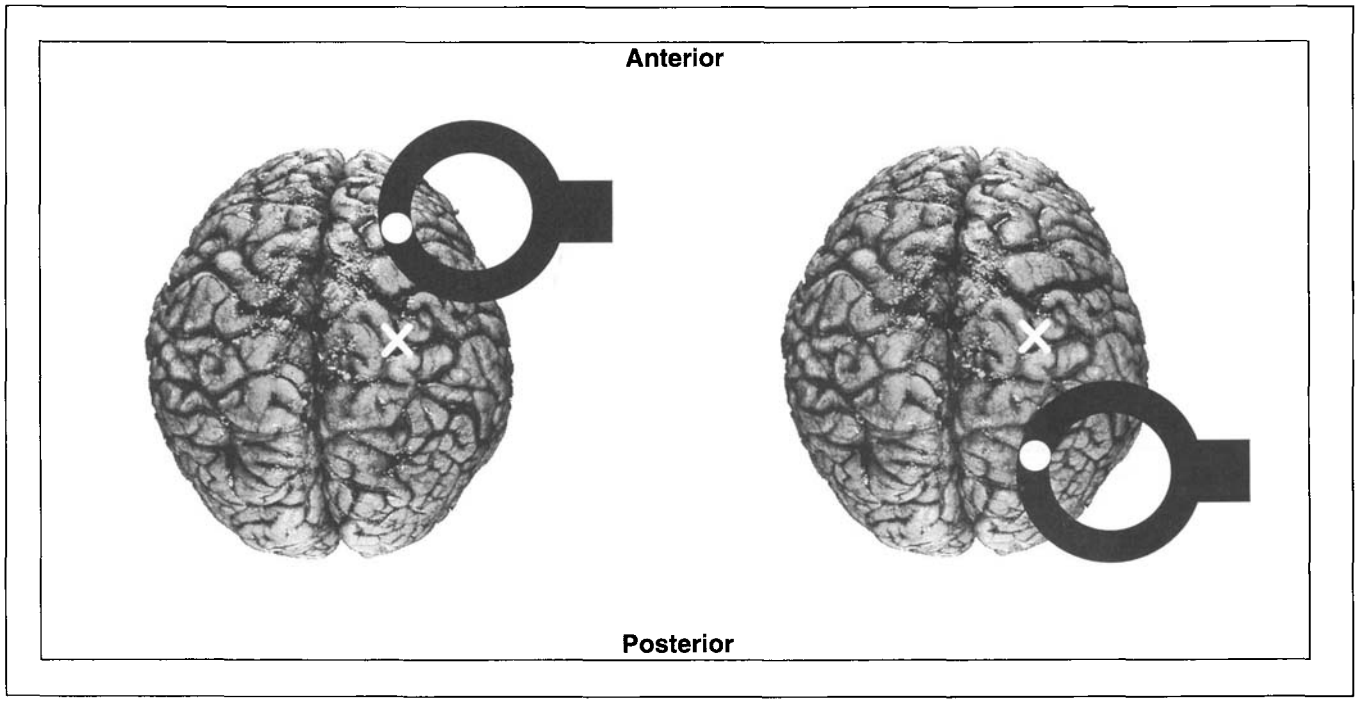

Figure 3. A schematic representation of the placements of the TMS coil on dorsal views of a human brain. The X represents the location of the motor cortex and each dot represents the location that was used as a landmark for coil positioning. The left half of the figure shows the placement of the coil for the SPFC condition and the right half of the figure shows the coil placement for the SPL condition.

human FEF, but rather to determine the influence of the FEF in generating voluntary and reflexive saccades. Future investigations will be aimed at localizing the anatomical structures involved in these delayed contralateral saccades by using a more focally active, figure-eight TMS coil with individual MRI scans with fiducial scalp markers.

Although the effects observed here may be due to disruption of other frontal areas involved in saccadic eye movements, such as the supplementary eye fields or the dorsolateral prefrontal cortex (Pierrot-Deseilligny, Israel, Berthoz, Rivaud, & Gaymard, 1993; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991), the pattern of results converge with our previous study in neurologic patients. In the study conducted on patients with lesions to the FEF (Henik et al., 1994), endogenous saccade latencies were inflated when eye movements were made toward the contralesional hemifield, and exogenous saccade latencies were inflated when saccades were made toward the ipsilesional visual field. This latter result was attributed to a disinhibition of the ipsilesional midbrain, which in turn inhibited the opposite colliculus. A similar pattern of results (i.e., slowing of contralateral saccades in the endogenous task and slowing of ipsilateral saccades in the exogenous task) was also found in the current study when TMS was over the SPFC. However, only the contralateral endogenous saccades were delayed, and the effects of prefrontal TMS on exogenous saccades were not statistically reliable. If chronic lesions of the FEF produce delayed ipsilesional exogenous saccades but TMS over the FEF does not, this would suggest that the effects of chronic lesions on ipsilesional exogeneous saccades reflect some plasticity developing after partial recovery.

Consistent with this interpretation are observations in the time course of the Sprague effect (Sprague, 1966). Wallace and colleagues produced contralesional neglect in cats with lesions of the occipito-parieto-temporal cortex (Wallace, Rosenquist, & Sprague, 1989, 1990). They then showed that lesions of the midbrain opposite the cortical lesion, which interrupted transcommissural projections from the substantia nigra pars reticulata to the superior colliculus on the same side of the cortical lesion, could produce improvement in the neglect. However this Sprague effect was typically delayed for an average of more than a week after the midbrain lesions. It is therefore perhaps not surprising that the transient cortical inactivation with TMS does not produce the same kind of reverse Sprague effect reported for chronic FEF lesions.

Although the influences of a TMS pulse are transient and produce only a brief disruption of cortical activity, it is notable that the effects of TMS over the SPFC on endogenous saccades occurred over a range of SOAs. It is now apparent that TMS over different cortical regions produce different magnitudes of effects. The impairments of visual perception following a TMS pulse to the occipital cortex are often brief (Amassian et al., 1989; but

see Beckers & Homberg, 1991), but TMS of other cortical areas has been shown to disrupt processing for relatively long intervals. For example, perception of contralateral tactile stimuli can be disrupted for up to 300 msec after a TMS pulse is delivered to the sensorimotor cortex, as well as up to 150 msec prior to the TMS pulse (Seyal, Masuoka, & Browne, 1992). Hypersensitivity to tactile stimuli can also be induced when a magnetic pulse is administered to the ipsilateral parietal cortex 50 msec prior to the delivery of a tactile stimulus (Seyal, Ro, & Rafal, 1995). In this latter situation, the influence of the TMS pulse not only affected the underlying cortex that was being stimulated but also had later influences on the activity in connected regions of the opposite hemisphere.

In addition to disrupting sensory processing for variable time intervals, TMS can also influence cortical structures that are involved in motor activity for considerably long time intervals. For example, electromyographic (EMG) recordings of the silent period following TMS of the motor cortex demonstrates that normal activity is disrupted for intervals of more than 150 msec (Fuhr, Agostino, & Hallett, 1991). A recent study by Muri et al. (1994) has also shown relatively long-lasting effects (at least 140 msec) of TMS on the supplementary motor area when executing sequential memory-guided saccades. The consistent effect of TMS across the SOAs on contralateral endogenous saccades suggests that TMS over the FEF can have prolonged effects. Furthermore, the execution of saccades has been shown to involve different components that can be programmed independently (Abrams & Jonides, 1988). The delayed saccades following TMS of the SPFC may be a result of the disruption of any of several stages in the execution of saccades, including the perceptual analysis of the go signal and preparation and programming of a saccade.

We have provided evidence that TMS of the prefrontal cortex (including the frontal eye fields) can delay endogenously generated saccades but does not influence reflexive visually guided saccades. This delay of endogenous saccades following TMS of the prefrontal region is most likely due to a disruption of activity in the frontal eye fields. TMS over the parietal lobe had no influence on saccades made in response to either type of go signal. These results provide converging evidence with PET and lesion studies indicating an important role of the frontal eye fields in generating voluntary eye movements.

METHODS

Subjects

A total of 10 subjects, 6 females and 4 males, participated in the experiment after giving informed consent. Two of the participants were investigators. None of the subjects had neurological disorders, and all had normal or corrected vision. The mean age of the subjects was 25.9. Approval to conduct the study was granted from the Veterans Administration Medical Center in Martinez, California, and from the University of California, Davis.

Apparatus

Transcranial magnetic stimulation was performed using a Cadwell Laboratories MES-10 stimulator (Kennewick, WA). The MES-10 stimulator at maximum intensity creates a 2.2 Tesla field with a shape determined by the configuration of the coil (Cadwell, 1990). Mapping of the cortex was performed to localize the motor cortex in each subject prior to the study using a figure-eight-shaped coil. Each component of the figure-eight coil measured 4.5 cm in diameter. A circular coil, which measured 9 cm in diameter, was then used during the saccade tasks at frontal and parietal locations based on this landmark. Because the click associated with a TMS pulse may cause hearing damage (Counter, Borg, Lofqvist, & Brismar, 1990; but see Pascual-Leone et al., 1992), all subjects wore sound attenuating ear plugs during the study.

Eye movement latencies were recorded using an Applied Science Laboratories Eye-Trac 210 infrared eye-tracking device (Bedford, MA). The digital output from the Eye-Trac 210 was interfaced to an Eye Movement Detection System created by Greg Laird Associates (Portland, OR). The eye movement detector provided on-line analysis of all eye movements and signaled when eye movements exceeded 60° second^{-1}.

An IBM-compatible personal computer was used to trigger the MES-10, to record the eye movement latencies, and for stimulus presentation. Millisecond (msec) timing, used to trigger the MES-10 and to measure the eye movement latencies, was achieved by setting the 8253 chip of the computer to millisecond ticks. The computer was connected to a NEC Multisync video graphics array (VGA) stimulus monitor. The timing of the visual displays was controlled by the vertical synchronization of the computer monitor at 16 2/3-msec intervals (60 Hz).

Functional Mapping of Motor Cortex

Prior to the start of the experiment, localization of the motor cortex, which was used as an anatomical landmark, was performed using a figure-eight coil. With this coil positioned over the motor cortex, it was often possible to obtain twitches from individual digits of the contralateral hand. After localizing the area of motor cortex that produced the most reliable, visibly robust contraction of the contralateral hand, scalp markings were then made on each subject. A mark was placed over the area of motor cortex representing the contralateral hand, over the area of cortex 5 cm anterior to the

hand area, as well over the area 5 cm posterior to it (see Figure 3).

After the scalp markings were made, the minimum intensity of TMS needed to produce twitches of the contralateral hand with the 9-cm circular coil was determined. Since TMS over the frontal cortex often produced facial twitches and blinks, it was not possible to have a predetermined, suprathreshold intensity that was comfortable for each subject. We therefore set the initial TMS intensity at 10% above motor threshold and then decreased the intensity, while staying above the threshold, until the subject was comfortable with the procedure. The range of intensities used during the experiment was between 34 and 60% of maximum output of the MES-10, which corresponded to TMS intensities between 1 and 10% above the visible motor threshold.

Stimuli and Procedure

The subjects were seated 57 cm from the computer monitor in a dimly and diffusely lit room. A cross, with each segment measuring 0.25°, served as the initial fixation point and was presented in the center of the monitor until the start of each trial. Two unfilled squares which measured 1.6° on each side were used as marker boxes and were present throughout the experiment. These boxes were centered at 10° to the left and right of the fixation point. All stimuli were white on a black background.

Following an intertrial interval of 2500 msec, the fixation point was removed and a go signal appeared either 400 or 600 msec later. These two interstimulus intervals (ISIs) were used as a precautionary measure to reduce the number of anticipation errors made as well as to alert the subject that the trial was about to begin. The go signals were either a 0.9° arrowhead (endogenous task) that was presented in the center of the display or a 1.1° asterisk (exogenous task) that was presented in one of the two boxes. The direction of the go signal was randomly determined and it was presented until a saccade was made (see Figure 4). The different go signal types were run in separate blocks for each subject, and the order of blocks was counterbalanced across subjects.

A TMS pulse was administered on each trial either 100 msec before (−100-msec condition), simultaneous with (0-msec condition) or 100 msec after (+100-msec condition) the onset of the go signal. Each of these three TMS

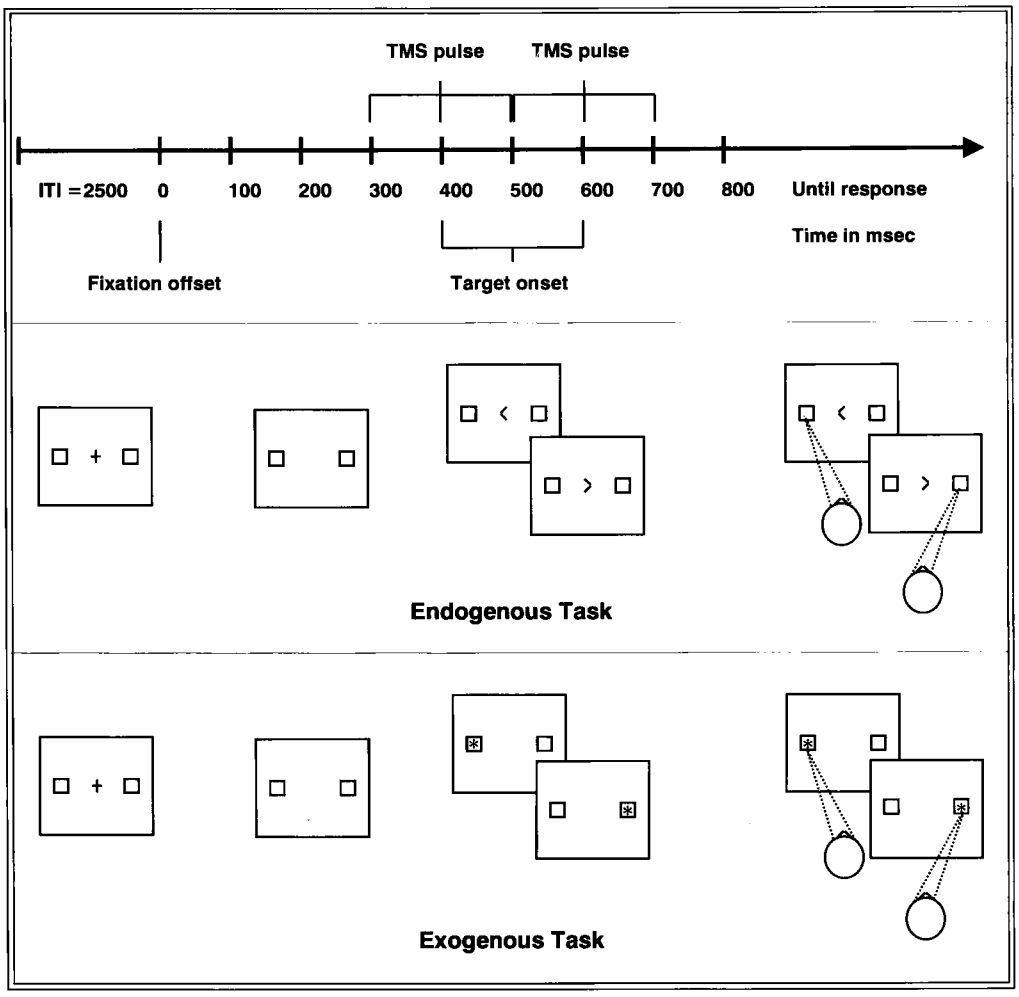

Figure 4. The time course of stimuli presentation (top panel) and the displays used in the two saccade conditions (bottom panels).

pulse to go signal SOAs was randomly presented an equal number of times within each block. The axis of the TMS coil was angled at approximately 90° from the midsagittal axis of the subject and was placed slightly anterior to the cortex 5 cm anterior (SPFC) or slightly posterior to the cortex 5 cm posterior (SPL) to the hand area of the motor strip (see Figure 3). This placement was used to avoid activation of the motor cortex. In a few subjects, however, we still observed occasional twitches of the contralateral hand during TMS of the SPFC. The order of TMS site was counterbalanced across subjects such that half the subjects received TMS over the SPFC first while the other half first received TMS over the SPL. In addition, half of the subjects were stimulated over the left hemisphere and half were stimulated over the right.

The subjects were instructed to keep their eyes on fixation until a go signal appeared. After the onset of the go signal, the subjects were instructed to make a saccade, as quickly and as accurately as possible, to the box that the arrowhead was pointing toward or to the box that contained the asterisk. Following the saccade, the subjects were told to return their eyes to the fixation point. All subjects were also instructed to suppress blinks during the trial and to ignore the TMS pulse as best as possible.

Trials with saccades made in the wrong direction or with saccade latencies slower than 1500 msec or faster than 100 msec were considered errors. These trials were excluded from analysis and were repeated later in the block. When such an error occurred, feedback was given to the subject in the form of a written message on the monitor. For trials with saccades made in the wrong direction or saccade latencies that were slower than 1500 msec, the message read "ERROR." For anticipation errors, a "TOO SOON" message was displayed.

All subjects performed the same number of correct trials per block in addition to the repeated error trials, which varied across subjects. A total of 12 correct trials was obtained as practice prior to the start of each of the four blocks (2 TMS sites × 2 go signal types). Within each block, the subjects first performed 24 correct trials without TMS (baseline condition) followed by 120 correct trials with TMS. The subjects were given four short breaks during the TMS trials. At the end of the set of trials with TMS, the subjects then completed another 24 correct baseline trials without TMS. A total of 20 correct trials for each condition with TMS pulses were obtained. For the baseline trials, a total of 48 correct trials per field (left and right) were collected for each go signal.

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Notes

1. Given that there were only five subjects in each hemisphere of TMS group, we did not have sufficient statistical power for a between-group analysis to adequately assess for possible hemispheric asymmetries. Such an analysis would be especially problematic given that there was a trend for a left-right field asymmetry for exogenous saccades without TMS.

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