

## The Location Probability Effects of Saccade Reaction Times Are Modulated in the Frontal Eye Fields but Not in the Supplementary Eye Field

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**The visual system constantly utilizes regularities that are embedded in the environment and by doing so reduces the computational burden of processing visual information. Recent findings have demonstrated that probabilistic information can override attentional effects, such as the cost of making an eye movement away from a visual target (antisaccade cost). The neural substrates of such probability effects have been associated with activity in the superior colliculus (SC). Given the immense reciprocal connections to SC, it is plausible that this modulation originates from higher oculomotor regions, such as the frontal eye field (FEF) and the supplementary eye field (SEF). To test this possibility, the present study employed theta burst transcranial magnetic stimulation (TMS) to selectively interfere with FEF and SEF activity. We found that TMS disrupted the effect of location probability when TMS was applied over FEF. This was not observed in the SEF TMS condition. Together, these 2 experiments suggest that the FEF plays a critical role not only in initiating saccades but also in modulating the effects of location probability on saccade production.**

**Keywords:** FEF, location probability, saccadic reaction time, theta burst TMS

### Introduction

Regularities can be found in many aspects of our visual world. Whether it be the signal pattern of the traffic light or the usual hiding corner employed by the traffic police, learning these predictive regularities can be advantageous in many circumstances. Numerous studies have demonstrated people's capability to learn and exhibit knowledge of regularities in the environment without subjective awareness (Chun and Jiang 1998; Fiser and Aslin 2001; Kristjánsson et al. 2001; Nakayama et al. 2004; Geng and Behrmann 2005). Eye movement studies have also shown that people can direct their eyes and attention to highly probable locations faster than to low-probability locations without employing an explicit strategy to do so (e.g., Farrell et al. 2009; Liu et al. 2010). Recently, Liu et al. (2010) found that sensitivity to external probabilities can be robust enough to offset the antisaccade cost, the extra reaction time (RT) it takes to prepare and execute an antisaccade relative to a prosaccade, in which eye movements are made away from and toward a visual stimulus, respectively. This was done with a new singleton search task where the frequency at which prosaccades were required was manipulated such that one

location was the target more often than others. Faster prosaccade RTs and higher antisaccade cost in the high-probability locations were seen. Moreover, when location probability was lowered, the antisaccade cost also changed in according to the magnitude of probability. Their results suggest that the antisaccade cost can be systematically changed with different levels of location probability. Together, this demonstrates the importance of probabilistic information in making simple decisions and its effect in modulating the antisaccade cost.

Neurophysiological studies have indicated a network of brain regions that are associated with tracking external regularities. Specifically, the superior colliculus (SC), supplementary eye field (SEF), and frontal eye field (FEF) tend to produce pretarget-related neural activity during saccade preparation (SC: Basso and Wurtz 1997, 1998; Dorris et al. 1997; SEF: Schlag-Rey et al. 1997; Connolly et al. 2005; Stuphorn and Schall 2006; FEF: Schall 1997; Bichot and Schall 2002; Sato and Schall 2003). Basso and Wurtz (1997) used a cuing paradigm to investigate how changing probability could alter SC activity in monkeys. These authors introduced probability by manipulating 1, 2, 4, or 8 possible saccadic targets to increase uncertainty. They found that as target probability increased, the neural activity in SC preceding the target selection also increased. Similarly, Dorris and Munoz (1998) manipulated target probabilities between different blocks and found that the neural firing rates in the target receptive fields also became higher. Such early probability-contingent activity in SC can be attributed to the particular eye movement that was about to be selected. These studies suggest an important role for SC in mediating the effect of probability in oculomotor behavior, and it remains possible that this pretarget SC activity might represent a preliminary selection from descending cortical influences (Basso and Wurtz 1997; Everling and Munoz 2000).

In the present study, we focused on the possible contributions of FEF and SEF to the location probability effects. The involvement of FEF and SEF in tracking external probabilities seems to be linked with their roles in saccade decision and preparation. That is, in order for probability to have an effect on eye movements, such probabilistic information must be taken into account throughout the stages of target selection and decision making (Sato and Schall 2003; Juan et al. 2004). In FEF, Sato and Schall (2003) found 2 types of neurons in macaque monkeys that selectively responded to either the singleton

regardless of the ultimate gaze shift or the saccade endpoint regardless of singleton location. The latter group of neurons could account for the different saccadic reaction times (SRTs) for these 2 types of response because these neurons had to select saccade endpoints depending on the trial type (i.e., prosaccade or antisaccade). This demonstrates that the 2 types of neurons can correspond to sequentially distinct visual processing, such as target and saccade selection. In addition, preparatory-related activities can be found in FEF with trained monkeys in an antisaccade task, and these signals in their unaltered form are sent directly to the SC (Everling and Munoz 2000). Functional magnetic resonance imaging blood oxygen level-dependent activity in FEF also can be used to predict SRT in humans (Connolly et al. 2005). Together, these findings suggest that the effect of location probability on SRT could be reflective of the neural firing rate within a subpopulation of neurons in the FEF. This may account for the role of FEF in mediating the effects of location probability because both target and endpoint selections are necessary for the benefit of location probability to surface.

Besides FEF, the SEF is also a good candidate for the mediation of the effect of external probabilities due to its functions related to conditional oculomotor learning rules (Chen and Wise 1995; Olson and Gettner 2002), reward or error monitoring (Stuphorn et al. 2000; Roesch and Olson 2003), smooth pursuit (Nyffeler et al. 2008), and antisaccades (Schlag-Rey et al. 1997; Curtis and D'Esposito 2003). Schall and colleagues proposed that the function of SEF is to influence behavior by biasing signals that project to other areas within oculomotor system, thereby serving as a monitoring control area (Stuphorn et al. 2000; Schall et al. 2002). More specifically, SEF may regulate saccade production by biasing the balance between gaze-holding and gaze-shifting signals, depending on prior information and task demand. These supervisory functions of SEF make it a likely location to code contextual information and exert its influence by way of projections to the FEF (Schall et al. 1993) or the SC (Shook et al. 1990).

The present study aimed to investigate whether FEF and SEF are critically involved in mediating the effects of external probability on an antisaccade task. Several studies have suggested a functional hemispheric asymmetry in the human FEF (Muggleton et al. 2003, 2010; Campana et al. 2007). For example, Campana et al. (2007) found that rTMS over the left FEF significantly reduced the priming effect of spatial positions. On the other hand, in visual search tasks, TMS has been applied over the rFEF to examine the timing of its involvement in oculomotor control (e.g., Juan et al. 2008). In the present study, the rFEF was chosen as the target of TMS stimulation due to its specialized role in oculomotor control. Previous studies have suggested that the enhanced performance (e.g., faster RT) from external probability can be related to visuospatial attention processes (Geng and Behrmann 2005) and motor preparation (Glimcher and Sparks 1992; Dorris and Munoz 1998). Since the time windows of these stages of processing and the exact timing of the effects of probability are still unclear, we adopted an offline TMS approach (repetitive TMS), using theta burst stimulation, to investigate the roles of rFEF and SEF without the requirement for temporal precision. Compared with single-pulse stimulation, the notable difference is that the duration of the theta burst TMS effect is longer (~20 min) and the result of a train of TMS pulses (for 20 s in this study). This can induce lasting disruptive effects on the stimulated region. With respect

to rTMS over SEF, recently, rTMS was used to investigate the role of this region in smooth pursuit control (Drew and van Donkelaar 2007; Nyffeler et al. 2008) and in target location processing in endogenously guided saccades (Rosenthal et al. 2008). These studies demonstrated that the human SEF does not solely function as an oculomotor output area but also as a higher order oculomotor area involved in complex processes (e.g., Stuphorn et al. 2010). Theta burst rTMS has been used to induce relatively long-lasting interference in order to better investigate the possible causal roles of FEF and SEF in task performance (Nyffeler et al. 2006; also see Huang et al. 2005, for an example of TMS in human motor cortex). It is hypothesized that if the rFEF and the SEF are essential for flexible adaptation to the location probability, a significant change in the magnitude of the probability effect should be observed when TMS disrupts rFEF or SEF activity. To our knowledge, this is the first study to apply theta burst rTMS over SEF to study the effect of disrupted SEF activity on oculomotor control and location probability in humans. Therefore, a second aim of this study was to investigate what kind of changes in saccadic response would occur when theta burst rTMS is applied over SEF.

## Materials and Methods

Experiment 1 and 2 shared the same materials, procedures, and design and only differed in the TMS site (Exp 1: rFEF; Exp 2: SEF).

### Participants

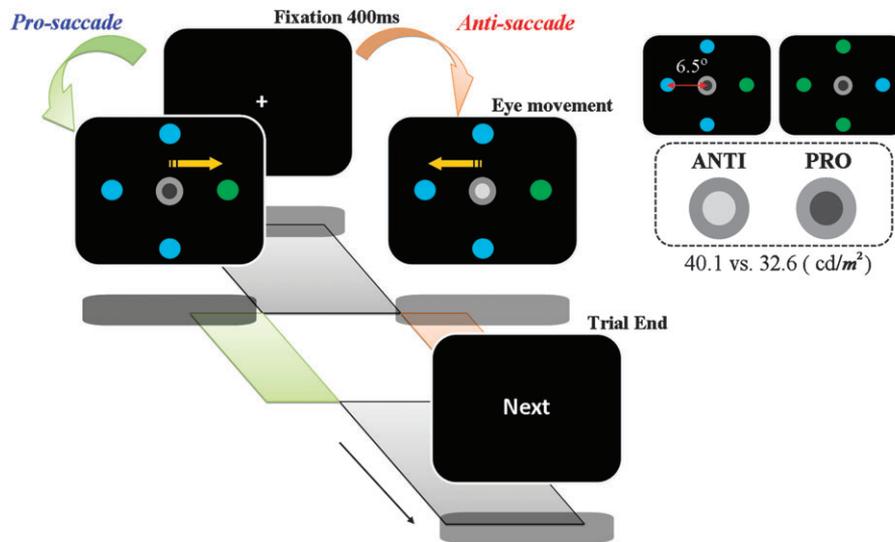
Sixteen undergraduate and graduate students from the National Central University (19–24 years old) participated in experiment 1, and an additional 16 new participants in experiment 2 to avoid explicit or implicit awareness of the statistical regularities. All participants had normal or correct-to-normal vision. Each participant received monetary payment for their participation upon completion of the experiment. Participants were not informed of the experimental design in terms of location probabilities until they completed the entire experimental session. All participants gave informed consent form prior to the experiment. The experiments were approved by the Institutional Review Board of the Chang-Gung Memorial Hospital, Taoyuan, Taiwan.

### Apparatus

Participants sat in a dimly lit room with their head stabilized by a chinrest. Stimuli were presented on a 19-inch color cathode ray tube monitor (View Sonic Professional Series P95f+), positioned 86 cm in front of the participants. The monitor had a spatial resolution of 1024 × 768 pixels and a refresh rate of 100 Hz. The computer was equipped with a RADEON 9600 SERIES display card manufactured by ATI Technologies Inc. The brightness of stimuli and background were measured by a ColorCAL colorimeter (Cambridge research systems). Eye movements were recorded from the left eye with an EyeLink II tracker (SR Research Ltd.). The task was programmed in Experimental Builder (SR Research Ltd). The sampling rate was set at 500 Hz, which provided one data point every 2 ms. Saccades were automatically identified when the eye velocity exceeded 30°/s and its acceleration exceeded 8000°/s<sup>2</sup>. Only the first saccade made by the participant on each trial was collected.

### Procedure

An eye-tracker calibration procedure was performed at the start of the experiment. This was followed by 80 practice trials, followed by the formal experimental sessions. Participants were instructed to perform the task as quickly and accurately as possible. Each trial started when participants fixated at the central fixation cross (0.5°) for 400 ms. A search display consisted of a saccadic indicator in the center, and 4 stimuli in the periphery were then presented (Fig. 1). Participants were



**Figure 1.** The fixation cross was presented for 400 ms and was followed by the target and the cue until participants responded or 2.5 s (whichever occurred first). Participants were instructed to make a prosaccade toward the colored singleton when the inner circle was darker than the outer concentric circle. When the inner circle was brighter than the outer one, participants needed to make an antisaccade away from the colored singleton (the arrows were not presented on the screen during testing).

instructed to make a single saccade of the type specified by the saccadic indicator. The saccadic indicator consisted of 2 concentric circles. If the inner circle was darker than the outer circle, participants were to perform a prosaccade to the colored singleton in the periphery. If the inner circle was brighter than the outer one, an antisaccade away from the colored singleton was required. After the completion of each trial, the computer displayed “Next” at the center of the display. Participants could either rest or press the space bar to continue onto the next trial at any time.

In the search display, the saccadic indicator (concentric circles  $2^\circ$ , contrast of brightness  $40.1/32.6 \text{ cd/m}^2$ , see Fig. 1 below) was always in the center and the 4 circles were  $6.5^\circ$  from the fixation cross at the left, right, top, and bottom positions. There were 2 versions of the singleton: blue (Commission International de l’Eclairage,  $x = 0.18$ ,  $y = 0.19$ ) among green ( $x = 0.27$ ,  $y = 0.51$ ) circles or green among blue circles. Colors in the array were approximately isoluminant (blue  $27.7 \text{ cd/m}^2$  green  $28.4 \text{ cd/m}^2$ ) and presented on a uniform black background ( $0 \text{ cd/m}^2$ ).

### Design

The experiment consisted of 2 blocks, one with no-TMS and one with TMS, with 194 trials in each block. Each block was assigned a roughly equal pairing of prosaccade and antisaccade probabilities (prosaccade vs. antisaccade: 98 vs. 96 trials). The manipulation of probability was applied only to the saccade endpoint location for prosaccade trials and not antisaccade trials (i.e., all locations were of equal likelihood when an antisaccade was required). In previous work, location probability was only manipulated on prosaccade trials. We found that latencies in the high-probability (75%) condition were lower than those in the low-probability condition (Liu et al. 2010). This result is robust although the underlying neural correlates are still unclear. Therefore, in the current study, we only manipulated location probability on prosaccade trials. In each block, 75% of prosaccade trials were made to the high-probability location and the remaining 25% of trials were evenly distributed to the other 3 low-probability locations. Therefore, each block consisted of an uneven distribution of prosaccade probabilities and an even distribution of antisaccade probabilities. Apart from the high-probability location, saccade directions were randomly assigned regardless of the saccade types. Prosaccade and antisaccade trials were interleaved (Olk and Kingstone 2003; Juan et al. 2008), which is thought to require that the programming of a prosaccade or antisaccade had to be withheld until participants had finished analyzing the central saccadic indicator. The order of trial types was randomized. Each block lasted ~20 min. This ensured that the experiment length did not exceed the expected duration of the TMS effect (Huang et al. 2005).

### Stimulation Site and TMS Protocol

A Magstim Super-Rapid Stimulator and a figure-of-8 coil were used to deliver TMS. The site for rFEF stimulation was located by using a simple saccade task during which TMS was delivered for 500 ms at 10 Hz over candidate sites anterior to the hand motor area in the right hemisphere using a grid of points separated from each other by 1 cm. The site that resulted in the longest saccade latencies was marked as target point for stimulation during the main task. The TMS locations identified were consistent with the locations in previous studies (Ro et al. 2002; Juan et al. 2008, see Fig. 2).

SEF was located by moving 3 cm rostrally and 0.5 cm laterally on the basis of the location previously reported for SEF in humans (Nyffeler et al. 2008, see Fig. 2). This was validated in 5 subjects for whom structural MRI scans were available using theBrainsight system. The coordinates of the SEF were determined by participants’ structural MRI with the Brainsight system (Rogue Research) in those where such scans were available. Participants wore goggles with a tracker attached, enabling them to be coregistered with their structural image using a mounted Polaris infrared tracking system (Northern Digital).

The sequence of control (no-TMS) and TMS blocks was counter-balanced across subjects. In the rFEF and SEF TMS conditions, theta burst TMS was applied at the beginning of both blocks. Participants then rested for 5 min (Hubl et al. 2008) before participating in the formal experiment. TMS pulses were applied in the continuous rTMS pattern as specified by Huang et al. (2005): participants received a total of 300 pulses within 20 s, 3 pulses were given at 50 Hz, and were repeated every 200 ms at 40% of maximum intensity. The maximum output of the TMS machine was 2 T. A fixed stimulation level was used because it has proven successful and replicable in many studies and over a wide range of tasks (e.g., Ashbridge et al. 1997; Rushworth et al. 2002; Muggleton et al. 2003, 2010; Hung et al. 2005; Ellison and Cowey 2007; Kalla et al. 2008; Chen et al. 2009) and because motor cortex excitability does not provide a good guide to TMS thresholds in other cortical areas (Stewart et al. 2001).

### Data Analysis

Eye movements were recorded as correct saccades when the eye landed within a computer-defined square boundary ( $2^\circ \times 2^\circ$ ) centered on the target. Saccade latency was defined as the time interval between target onset and the initiation of a saccade. To identify outliers, a boxplot method was used to find data that were 1.5 times the interquartile lower than the first quartile (subtracting the first quartile from the third quartile) or 1.5 times the interquartile range higher than

the third quartile. Less than 5% of trials were excluded from further analysis. Trials from both no-TMS and TMS conditions were categorized under 2 independent variables: saccade type (prosaccade and antisaccade) and location probability (high and low). Note that the high-location probability included prosaccades made to the high-probability location (75% of all prosaccade trials) and antisaccades made “away” from the high-probability location (25% of all antisaccade trials). The low-probability location condition consisted of prosaccades made to the 3 low-probability locations (totaling 25% of all prosaccade trials) and antisaccades made away from the 3 low-probability locations (totaling 75% of all antisaccade trials).

To ensure that our participants were performing the task accurately, we set 2 criteria for performance before we conducted data analysis. The first criterion for exclusion was whether or not participants showed a positive probability effect (mean SRT of prosaccade made to low probability minus mean SRT of prosaccade made to high probability). Participants who did not have a positive probability effect were unaffected by the relevant experimental manipulation and so were excluded on this basis. Second, participants who showed a bias for a certain saccade type (prosaccade or antisaccade) were also excluded from analysis. This could be observed from accuracy and RT, as a bias would result either in a highly unequal accuracy between prosaccade and antisaccade or a delayed RT for one type of saccade. Based on these 2 criteria, 3 participants were excluded from Experiment 1 and 2 participants were excluded from Experiment 2.

## Results

### Effects of TMS and Probability

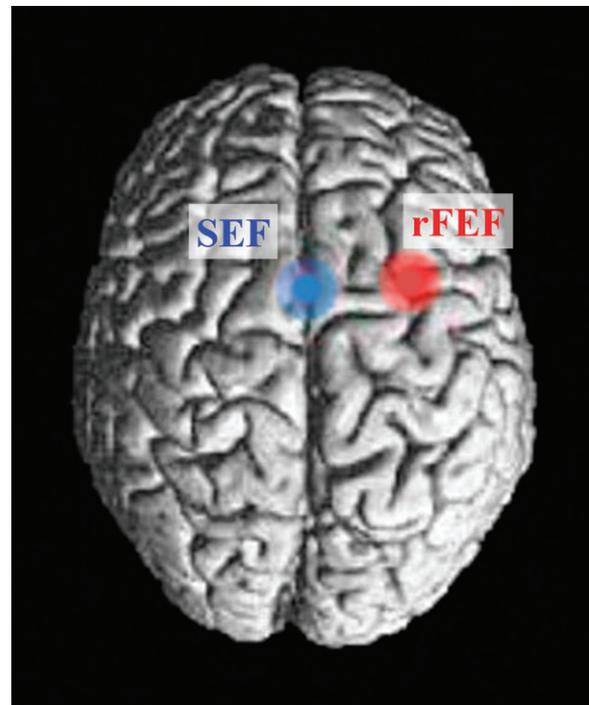
#### Experiment 1 (rFEF)

Mean percent correct of total trials in control and TMS conditions were 83.7% (pro = 87.9%, anti = 79.4%, paired  $t_{12} = 6.2$ ,  $P < 0.001$ ) and 82.2% (pro = 85.7%, anti = 78.3%, paired  $t_{12} = 4.5$ ,  $P = 0.001$ ). A three-way repeated measures analysis of variance (ANOVA) was performed to investigate whether TMS, saccade type, and location probability had an effect on saccade latencies (see Fig. 3). There was a significant main effect for TMS ( $F_{1,12} = 15.8$ , mean square error (MSE) = 7673.3,  $P < 0.01$ ), saccade type ( $F_{1,12} = 14.9$ , MSE = 10082.8,  $P < 0.01$ ), and probability ( $F_{1,12} = 6.5$ , MSE = 2588.4,  $P < 0.05$ ). There was also a significant interaction between saccade type and probability ( $F_{1,12} = 21.3$ , MSE = 1180.7,  $P < 0.01$ ), which replicated our previous findings (Liu et al. 2010).

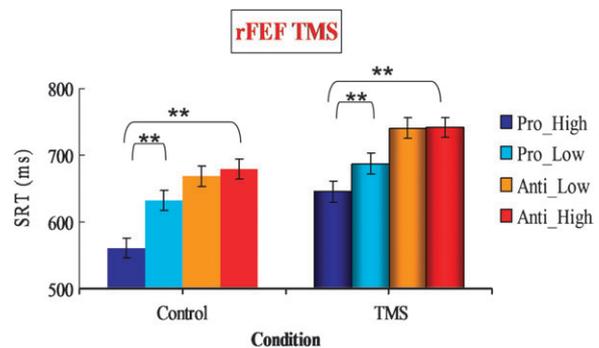
The effect of TMS indicated that saccade latencies were on average slower when TMS was applied (no-TMS vs. TMS: 635.5 vs. 703.9 ms). For the significant interaction (saccade type  $\times$  probability), post hoc analyses revealed that the RT difference between prosaccades and antisaccades was significant only in the high-probability locations (no-TMS:  $t_{12} = -5.4$ ,  $P < 0.01$ ; TMS:  $t_{12} = -4.1$ ,  $P < 0.01$ ) but not in the low-probability locations (no-TMS:  $t_{12} = -2.1$ ,  $P > 0.05$ ; TMS:  $t_{12} = -2.2$ ,  $P > 0.05$ ). RTs for prosaccade trials in the high-probability locations were faster than those in the low-probability locations (no-TMS:  $t_{12} = 5.3$ ,  $P < 0.01$ ; TMS:  $t_{12} = 3.7$ ,  $P < 0.01$ ), which confirmed the facilitatory effects of location probability (Geng and Behrmann 2005; Liu et al. 2010). These results were consistent across the no-TMS and TMS conditions, which suggested that the modulation of antisaccade cost was not due to a nonspecific general effect of TMS.

#### Experiment 2 (SEF)

Mean percent correct of total trials in the control and TMS condition were 84.6% (pro = 86.5%, anti = 82.7%, paired  $t_{13} = 2.05$ ,  $P > 0.05$ ) and 83.1% (pro = 86.1%, anti = 80.1%, paired



**Figure 2.** Sites of the TMS stimulation shown on an axial section on a normalized template of the human brain.



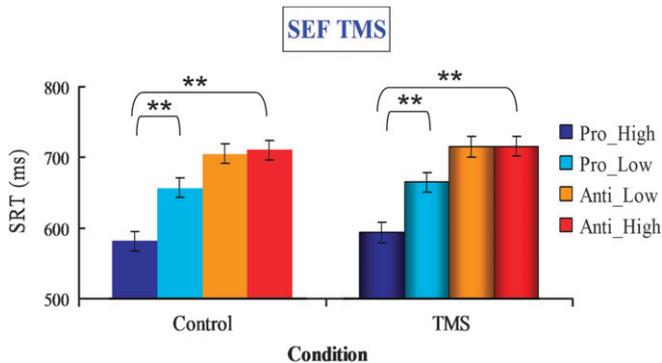
**Figure 3.** Experiment 1 results (rFEF TMS). Mean saccadic RTs are plotted as a function of TMS, saccade type, and probability. The bars with shadow indicate the TMS conditions. Blue tones indicate prosaccade trials and red/orange indicates antisaccades. SRTs of TMS condition were significantly longer than the control condition. Error bars represent the standard error of the mean. \*\*indicates significant  $P$  values less than 0.01.

$t_{13} = 4.05$ ,  $P < 0.01$ ), respectively. Similar to Experiment 1, we conducted a three-way repeated ANOVA with factors of TMS, saccade type, and probability on saccade latencies (see Fig. 4). The analysis yielded a significant effect of saccade type ( $F_{1,13} = 13$ , MSE = 16439.2,  $P < 0.01$ ) and probability ( $F_{1,13} = 17$ , MSE = 2063.9,  $P < 0.01$ ). We also observed a significant interaction between saccade type and probability ( $F_{1,13} = 36.1$ , MSE = 1127.4,  $P < 0.01$ ), whereas all other interactions were not statistically significant. Post hoc analyses for both no-TMS and TMS conditions revealed that the RT difference between prosaccades and antisaccades was significant in the high-probability locations (no-TMS:  $t_{13} = -4.8$ ,  $P < 0.01$ ; TMS:  $t_{13} = -6.2$ ,  $P < 0.01$ ), which reflected the same pattern as Experiment 1. Moreover, RTs for prosaccade trials in the high-probability locations were faster than those in the low-probability locations (no-TMS:  $t_{13} = 7.5$ ,  $P < 0.01$ ; TMS:  $t_{13} = 6$ ,  $P < 0.01$ ).

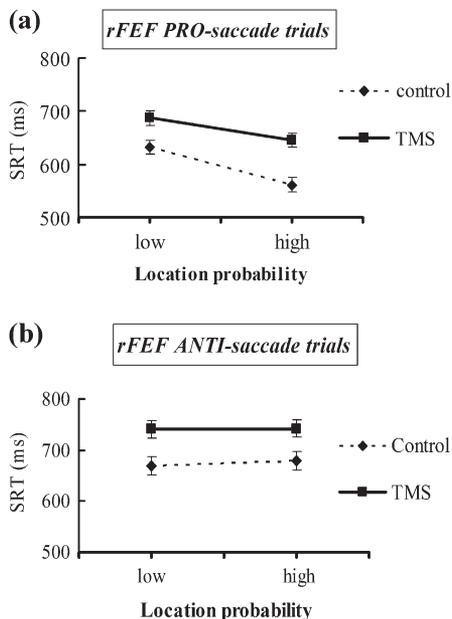
## Effect of TMS on Prosaccades

### Experiment 1 (rFEF)

In order to clarify the TMS and probability effects, only prosaccade trials were used in the following analyses. Two-way repeated measures ANOVA with factors of TMS and probability was performed on prosaccade RT measures (Fig. 5*a*). This revealed a significant main effects of TMS ( $F_{1,12} = 15$ , MSE = 4136,  $P < 0.01$ ) and of probability ( $F_{1,12} = 26.5$ , MSE = 1570.3,  $P < 0.01$ ) as well as a significant interaction between them ( $F_{1,12} = 6.6$ , MSE = 448.3,  $P < 0.05$ ). Post hoc analysis showed that RTs from the TMS condition were significantly slower than those from the no-TMS condition in both low-probability locations ( $t_{12} = 2.9$ ,  $P < 0.05$ ) and high-probability locations ( $t_{12} = 4$ ,  $P < 0.01$ ). It is noteworthy that the interference effect



**Figure 4.** Experiment 2 results (SEF TMS). Mean saccadic RTs as a function of TMS, saccade type, and probability. The bars with shadow indicate the TMS conditions. Blue indicates prosaccade trials, while colored/orange indicates antisaccades. Error bars stand for the standard error of the mean. \*\*indicates significant  $P$  values less than 0.01.



**Figure 5.** Data of mean prosaccade and antisaccade RT in Experiment 1 (rFEF TMS). Mean SRTs are plotted as a function of probability (high vs. low) and TMS application (control vs. TMS). (a) Mean saccadic RTs of prosaccade (b) mean antisaccade SRTs. Note that the high and low probabilities here represent the probabilities associated with the target singleton locations, which cued the participants to saccade away from the singleton. Error bars represent the standard error of the mean.

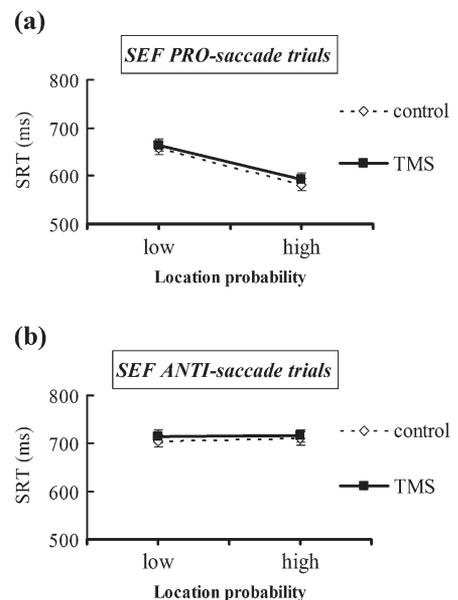
of TMS was larger in the high-probability locations than in the low-probability locations, which was the main cause of the significant interaction ( $t_{12} = -4.8$ ,  $P < 0.01$ ). Therefore, although rFEF TMS prolonged RTs across all conditions, its interference was greater on the prosaccade trials to the high-probability locations. In addition to prosaccade trials, we also performed the same repeated measures ANOVA on antisaccade trials. Two-way ANOVA was performed with factors of TMS and probability (Fig. 5*b*). There was a significant main effect of TMS ( $F_{1,12} = 13.6$ , MSE = 4347.8,  $P < 0.01$ ) but no significance for probability ( $F_{1,12} < 1$ , MSE = 2199,  $P > 0.05$ ) or an interaction between the 2 factors ( $F_{1,12} < 1$ , MSE = 769,  $P > 0.05$ ).

### Experiment 2 (SEF TMS)

Two-way repeated measures ANOVA with factors of TMS and of probability on prosaccade RT (Fig. 6*a*) only showed a significant main effect of probability ( $F_{1,13} = 80.9$ , MSE = 934.4,  $P < 0.01$ ). Unlike Experiment 1, there was no significant interaction between TMS and location probability ( $F_{1,13} < 1$ , MSE = 757.1,  $P > 0.05$ ). Post hoc analyses showed that RTs from both no-TMS ( $t_{13} = 7.5$ ,  $P < 0.01$ ) and TMS ( $t_{13} = 6$ ,  $P < 0.01$ ) conditions were faster in the high-probability location than in the low-probability locations. A two-way ANOVA on antisaccade RTs (Fig. 6*b*) did not yield any significant effect of TMS ( $F_{1,13} < 1$ , MSE = 4631.6,  $P > 0.05$ ), location probability ( $F_{1,13} < 1$ , MSE = 2257,  $P > 0.05$ ), nor an interaction ( $F_{1,13} < 1$ , MSE = 839.1,  $P > 0.05$ ).

### Probability in Prosaccades and Antisaccades

We also investigated whether the effect of probability would transfer to antisaccade trials. If the effect of probability mostly occurs at the stage of saccade motor preparation, we would expect to observe a benefit in both prosaccades and



**Figure 6.** Mean prosaccade and antisaccade RTs in Experiment 2 (SEF TMS). Mean SRTs are plotted as a function of probability (high vs. low) and TMS application (control vs. TMS). (a) Mean prosaccade SRTs (b) Mean antisaccade SRTs. Note that the high and low probabilities here represent the probabilities associated with the target singleton locations, which cued the participants to saccade away to the opposite side. Error bars represent the standard error of the mean.

antisaccades when they are made to the high-probability location. We compared RTs from antisaccades made to the high-probability location with those made to other locations. The results showed that the effect of probability was only present in prosaccade trials and not in antisaccade trials. This was true in the no-TMS (Exp. 1:  $t_{12} = 0.03$ ,  $P > 0.05$ ; Exp. 2:  $t_{13} = -0.05$ ,  $P > 0.05$ ) and TMS conditions (Exp. 1:  $t_{12} = -1.42$ ,  $P > 0.05$ ; Exp. 2:  $t_{13} = -0.1$ ,  $P > 0.05$ ) of both Experiment 1 and 2. This dissociation between the effects of probability on prosaccades and antisaccades successfully replicated our previous findings using the same paradigm (Liu et al. 2010).

## Accuracy

### Experiment 1 (rFEF)

For accuracy measures, a three-way repeated measures ANOVA was applied to examine the effect of TMS, saccade type, and location probability. There was a significant main effect of saccade type ( $F_{1,12} = 9.1$ ,  $MSE = 0.0043$ ,  $P < 0.05$ ) and location probability ( $F_{1,12} = 15.5$ ,  $MSE = 0.0092$ ,  $P < 0.01$ ). The TMS main effect approached significance ( $F_{1,12} = 3.7$ ,  $MSE = 0.0041$ ,  $P = 0.08$ ). No interaction was significant. Post hoc analyses further revealed that the effect of saccade type was mainly driven by an increased error rate in antisaccades to the high-probability location, relative to prosaccades to the high-probability location. This pattern was true in the TMS ( $t_{12} = 3.9$ ,  $P < 0.01$ ) condition but not in the no-TMS ( $t_{12} = 1.7$ ,  $P = 0.11$ ) condition. Note that our previous work using this paradigm (Liu et al. 2010) has already ruled out the possibility of speed-accuracy trade-off in explaining the behavioral results. Therefore, the nonsignificant no-TMS result here is most likely a reflection of the decreased number of trials in this study. This indicated that the significant antisaccade cost found in high-probability locations cannot be simply explained by speed-accuracy trade-offs.

### Experiment 2 (SEF)

Experiment 2 revealed a significant main effect of location probability ( $F_{1,13} = 13.2$ ,  $MSE = 0.004$ ,  $P < 0.01$ ). The effect of TMS ( $F_{1,13} = 2.3$ ,  $MSE = 0.006$ ,  $P > 0.05$ ) and saccade type ( $F_{1,13} = 1.77$ ,  $MSE = 0.009$ ,  $P > 0.05$ ) was not significant. One interaction (saccade type  $\times$  location probability) was significant ( $F_{1,13} = 6.8$ ,  $MSE = 0.007$ ,  $P < 0.05$ ), while other interactions were not.

## Discussion

Experiment 1 showed that SRTs across all conditions and saccadic types were prolonged by the rFEF TMS. The TMS created a temporary interference effect in rFEF, which delayed saccade latency in both prosaccades and antisaccades. This disruptive effect of TMS was more pronounced for prosaccades. Notably, the delay effect was larger in magnitude for the high-probability locations. This key observation indicates that the TMS indeed interfered with the magnitude of the probability effect and suggests a critical role for rFEF not only in initiating saccades but also in the effects of probability when it is relevant to the generation of saccades.

Experiment 2 used the same paradigm and applied TMS over SEF. In contrast to our observations in Experiment 1, here we did not see an interaction between TMS and probability in saccade latency. Thus, the present data suggest that SEF is not

causally involved in the effects of probabilistic information on saccade generation.

### rFEF and Location Probability

The facilitatory effect of external probability on motor preparation has been well documented (e.g., Dorris and Munoz 1998; Liston and Stone 2008) and can be seen in the increased level of pretarget activity in the SC prior to the execution of motor responses (Dorris and Munoz 1998). Our results suggest an additional level of facilitation that is likely to be a component of visual selection. This is because in Experiment 1, we observed a faster RT in prosaccades to the high-probability location but not in antisaccades. Since these 2 types of eye movements were directed toward the same high-probability location, they essentially shared the same motor plans. Thus, an enhancement in motor preparation should equally facilitate prosaccades and antisaccades to the high-probability location. Our observation of a dissociable effect of probability between prosaccades and antisaccades in Experiment 1 therefore suggests that other possible factors such as visual selection could also be contributing to the probability effect in addition to motor preparation. Electrophysiological studies with high temporal resolution have confirmed that probabilistic information may be available both during an early stage and a late response preparation stage (Gehring et al. 1992). Since our task requires participants to make voluntary saccades, the probability enhancement should not be limited to motor preparation only. The high-location probability is likely to make visual neurons of the FEF showing greater sensitivity when the singleton occurs at the highly probable location. The sensitized visual-sensitive neurons then send information to the motor neurons in the FEF, the effect of which may be an elevation of pretarget activity for motor preparation. The mechanisms of location probability may possibly be implemented through recruitment of visual sensitive and motor neurons in the FEF in a serial manner (e.g., Schall and Thompson 1999). Other researchers have also speculated on other origins of the probability enhancement effect at the visual selection stage, in tasks involving attentional disengagement (Fischer 1987), sensory facilitation (Reulen 1984), or fixation disengagement (Cavegn and d'Ydewalle 1996). Indeed, from these studies, the proposal is that oculomotor control is implemented through 2 independent form of decision: attentional decisions that assign value to a specific source of information and motor decisions (Gottlieb and Balan 2010). The early activity involved in the attentional decision occurs prior to pretarget saccadic activity and is independent of various properties of actions. Furthermore, Gottlieb and Balan (2010) suggest that the encoding of visual selection for attentional decisions can interact with information related to motor selection in saccade-related neurons. Though the proposal is made in relation to lateral intraparietal area (LIP), neurons of FEF also have receptive fields that encode visual and saccadic locations in a similar manner as in the LIP. Therefore, we suggest that the probability effect needs to be accounted for not only in relation to the later stage of motor preparation but also for decisions concerning the assignment of attention.

The finding that the rFEF can be affected by higher cognition, such as accumulation of probabilistic evidence, has also been reported by Gold and Shadlen (2000, 2003). These authors trained monkeys to make a directional judgment about a dynamic random-dot motion and indicate the judgment with

an eye movement to a visual target. Electrical stimulation was delivered over monkeys' FEF and was applied during the decision formation period. These microstimulation-evoked saccades tended to deviate toward the direction of the monkey's ultimate choice. Moreover, the magnitude of the deviation, even when measured early in the decisional processes, depended heavily on the motion strength and viewing time. Their results imply that, under certain conditions, decision development and motor preparation can share the same level of neural organization. Importantly, if the decision-making process is not linked to a particular action, such as an eye movement response, the involvement of the rFEF becomes considerably less. This is in line with the findings here as our manipulation of location probability was contingent upon saccade responses.

Some of the pioneering work on the SC has suggested that the function of the collicular buildup neurons may possibly be the integration of a variety of oculomotor signals and serving as a final decision maker that leads to the initiation of a saccade (Sommer and Wurtz 2000). The aim of the present study was to probe areas from the higher hierarchical levels of the oculomotor system that send signals to the SC, where pretarget collicular activity is often observed. Recent studies have argued that SC activity is not only primarily involved in generating and orienting saccades but is also affected by uncertainty (Basso and Wurtz 1997) and saccadic probability (Dorris and Munoz 1998). Everling and Munoz (2000) trained monkeys to perform an interleaved antisaccade task and observed higher stimulus-related FEF activity in prosaccade trials. Most importantly, FEF neurons that projected directly to the SC showed a similar pattern of pretarget discharge rate as other FEF neurons that did not directly communicate with the SC. This finding demonstrated that the direct descending pathway from the FEF to the SC carried preparatory set-related activity for prosaccades and antisaccades. It is plausible that the rFEF efferent neurons conveyed both intention and readiness signals to the SC. Furthermore, Sommer and Wurtz (2000) suggested that the delay signals from the FEF to the SC could relate to cognitive processing, in particular decisions of an appropriate saccadic response. Given that the SC is the final stage of processing in the oculomotor system, it is likely to receive probability-related signals from the rFEF and assert such cognitive influence by directly accessing the reticular formation premotor neurons.

Previous work by Nakayama and colleagues showed that repetition of the target position primes subsequent trials (Maljkovic and Nakayama 1996; Kristjánsson et al. 2001). In our previous work (Liu et al. 2010), we used the same task as was used here to address this issue and showed that the repetition priming effect could not explain the probability effect (see also Geng and Behrmann 2005). Therefore, we think this probability effect is not due to trial by trial priming but rather a contextual priming that accumulates across trials. This contextual priming guides visual selection/visual attention to meaningful regularities and invariant features in the environment. This allowed participants to be more sensitive to target location that was embedded among an array of distracters. That is, the probability effect is not simply constrained to the priming of location.

### ***The Effect of rTMS on rFEF***

In this study, we utilized the disruptive effect of rTMS to test whether rFEF and SEF are critical to the facilitatory effect of

location probability. The source of such theta burst TMS effect, especially in rFEF, is worth mentioning. At the cellular level, TMS induces a mixture of facilitatory and depressing effects on synaptic transmissions (Huang et al. 2005; Nyffeler et al. 2006). Physiological studies have identified characteristics of 2 main subpopulations within the rFEF, which selectively code either for the singleton or the saccade endpoint. It appears that location probability is contingent on the location of a singleton and not just the direction of saccades. Sato and Schall (2003) suggested that the saccadic endpoint selection time of movement neurons varied with SRT across trials in both prosaccades and antisaccades. Theta burst TMS caused a common delay of saccade generation across all conditions, and this delay could be labeled as interference with the movement neurons. In addition, the length of the delay was larger in the high-probability location than the low-probability location. The additional delay can be attributed to the greater TMS interference on neurons that coded the singleton locations.

In the context of neural firing rate, the TMS-induced delay can be viewed as the consequence of a reduction in the neural firing rate that contributed to the high-probability location effect. Given the evidence that movements are initiated only if the neural activity reaches a specific and constant threshold activation level (Hanes and Schall 1996), it is possible that the prolonged SRT (induced by TMS) was a result of a slower growth of drift rate to the threshold. Similarly, in the high-probability locations, the drift rate to the threshold of the prosaccade diminished even more. In other words, TMS could have suppressed the higher firing rates that were associated with the high-probability locations down to a level that was similar to other less probable locations. The discharge rate of the movement neurons, representing the 4 saccadic locations, may compete each other to reach the fixed threshold. The one first to reach the threshold will initiate a saccade. Thus, the conflict of neural signals has to resolve at a "winner-take-all" junction in the rFEF.

It should be noted that applying offline theta burst TMS can possibly produce a distal effect that comes from other areas of the processing loop besides the primary area of stimulation. Though this distal effect may exist in the rFEF and SEF TMS experiments, we still observed a TMS effect in our rFEF experiment, as well as a functional distinction between rFEF and SEF. Therefore, although a distal TMS effect may exist, it cannot account for the entirety of our results here, and it remains possible that the location probability can be processed in the rFEF without accessing the arbitrary association learning in the SEF. Note that we do not intend to suggest the rFEF as the neural locus for learning all types of probability. The results here simply suggest that the rFEF is critical in processing the probability of spatial locations. It is certainly possible that the rFEF is a part of a larger network, such as the frontoparietal attentional loop, that is critical in learning and mediating the effect of probability (e.g., Chao et al. 2010).

### ***SEF***

In Experiment 2, we did not observe an effect of TMS delivered over SEF on the effect of location probability. Several studies concerning the SEF's functional roles have observed high SEF activity when rule learning occurs in both a spatial and

nonspatial manner and suggested that the SEF plays a critical role in acquiring rules about the environment (e.g., Olson et al. 2000; Olson and Gettner 2002). The current findings do not seem to be in line with these findings. It is worth noting, however, that the present orienting paradigm is very direct in terms of saccade commands and, therefore, may be quite different from the delayed eye movement tasks that previous studies have used, which required some use of the short-term memory and might involve different cognitive processes. Indeed, Chen and Wise (1995) have also suggested that the SEF is more involved in the nonspatial tasks, in which successful performance is mostly determined by abstract rules. In contrast, FEF receives information from the SEF and directly promotes the finer adjustment of eye movements. This perhaps explains the dissociation between the rFEF and SEF here as our manipulation of probability was purely spatial and required precise eye movements. In addition, studies have demonstrated experience-dependent plasticity in the FEF (Bichot et al. 1996) and suggested a competitive mechanism in the FEF for topographic representation of features in different locations (Schall and Hanes 1993). Therefore, it is possible that location probability can be processed in the rFEF without accessing the arbitrary association learning in the SEF. In addition to that, there are several possible explanations for this absence of effects of SEF stimulation. First, microstimulation in the SEF during a saccade task can induce different effects, such as inhibiting neuronal activity in the FEF, delaying movements, or detecting errors (e.g., Stuphorn et al. 2000). This is likely due to the fact that the SEF, like many other parts of the frontal cortex, consists of different populations of neurons that are functionally different. Thus, the stimulus of interest to these neurons is more ambiguous than the FEF. Second, the location probability can be treated as a learned association between singleton location and saccade direction, and monkey physiological studies have shown that these associations can be coded by FEF neurons (e.g., Sato and Schall 2003). Therefore, it is possible that the location probability effect can simply be mediated by the rFEF without direct involvement of the SEF. Finally, another important factor to consider is the visuospatial aspect of the present study. There has been evidence suggesting that changes in SEF activity only occur when learning nonspatial information (Chen and Wise 1995). These authors proposed that the SEF is perhaps more involved in nonspatial actions than spatially directed action. This would explain the results of Experiment 2 because location probability in the present paradigm is contingent on singleton locations. Therefore, coding location probability would also require coding relevant spatial information. Following from Chen and Wise's (1995) suggestion, it is possible that the SEF could still assert an influence over saccade latencies by being involved in tracking nonspatial probabilities. For example, saccade trial-type probability, which denotes the probability ratio between interleaved prosaccade and antisaccade trials, is one type of external probability that does not involve spatial regularities. Therefore, it is possible to manipulate the ratio between prosaccade and antisaccade trials yet still maintain an equivalent ratio between all saccade locations. Studies have shown that an equivalent ratio of prosaccade and antisaccades can eliminate the antisaccade cost (Juan et al. 2008), while an unbalanced ratio can facilitate the highly probable saccade type and slow down the less probable saccade for prosaccade and antisaccades alike. If the SEF is more sensitive to

nonspatial information, we may be able to observe TMS-induced interference over the SEF when the task involves nonspatial probabilities, such as saccade types. Future research should address whether the SEF is critical to the processing of other types of nonspatial probabilities.

### Conclusions

The present study used a saccade task to investigate the neural mechanisms underlying the effects of probability on human oculomotor control. This study is the first to adopt a TMS approach to functionally probe the neural basis of the effects of probability on saccade behavior. We observed disruption of the effect of location probability when TMS was applied to rFEF but not SEF. TMS over the rFEF also delayed saccade triggering, which is consistent with previous reports of the effects of TMS over this area. These findings suggest that rFEF is not only critical in initiating saccade readiness and intention but is also important in mediating the effect of location probability. This is consistent with the known functions of the FEF, which consist of reorienting attention and preparing saccadic motor programs when monitoring singleton-saccadic location association. rFEF is likely to be one of the areas in the network that is involved in the manifestation of the effects of probability information on motor output and future work aimed at delineating the network of areas critical in this process would be beneficial.

### Funding

National Science Council, Taiwan (97-2511-S-008-005-MY3, 99-2410-H-008-022-MY3, 96-2413-H-008-001-MY3, 98-2410-H-008-010-MY3, 98-2517-S-004-001-MY3, 97-2511-S-008-008-MY5); UK Medical Research Council (to N.G.M.); National Science Council, Taiwan (98-2918-I-008-011) and the Fulbright scholarship, Taiwan and USA (to C.H.J.).

### Notes

We are grateful to W. J. Kuo, N. Leveridge, N. S. Yen, and Y. Y. Yeh for their comments on the manuscript. *Conflict of Interest*: None declared.

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