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The Role of the Frontal Eye Fields in Oculomotor Competition: Image-Guided TMS Enhances Contralateral Target Selection

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In order to execute a correct eye movement to a target in a search display, a saccade program toward the target element must be activated, while saccade programs toward distracting elements must be inhibited. The aim of the present study was to elucidate the role of the frontal eye fields (FEFs) in oculomotor competition. Functional magnetic resonance imaging-guided single-pulse transcranial magnetic stimulation (TMS) was administered over either the left FEF, the right FEF, or the vertex (control site) at 3 time intervals after target presentation, while subjects performed an oculomotor capture task. When TMS was applied over the FEF contralateral to the visual field where a target was presented, there was less interference of an ipsilateral distractor compared with FEF stimulation ipsilateral to the target's visual field or TMS over vertex. Furthermore, TMS over the FEFs decreased latencies of saccades to the contralateral visual field, irrespective of whether the saccade was directed to the target or to the distractor. These findings show that single-pulse TMS over the FEFs enhances the selection of a target in the contralateral visual field and decreases saccade latencies to the contralateral visual field.

Keywords: frontal eye fields, oculomotor capture, saccade, target selection, transcranial magnetic stimulation

Introduction

For successful goal-directed behavior in everyday life, it is crucial to attend relevant stimuli in the visual field while ignoring distractor elements. The oculomotor system is an excellent model for the study of this competition between different elements, because the outcome of the competition is directly reflected in the endpoint of an eye movement.

The frontal eye fields (FEFs) are hypothesized to play an important role in oculomotor competition (Clementz et al. 2007). Transcranial magnetic stimulation (TMS) studies on the role of the FEFs in oculomotor competition have used the antisaccade task, in which participants are instructed to generate a saccade to an imaginary point opposite to a peripheral visual stimulus (Hallett 1978). An automatically evoked saccade (prosaccade) to this visual element should be inhibited and a volitional saccade (antisaccade) should be triggered in the opposite direction. Healthy participants typically make erroneous prosaccades to the visual element in around 20% of trials (Everling and Fischer 1998; Tatler and Hutton 2007). Application of TMS over the FEFs increases the latencies of antisaccades (Muri et al. 1991; Terao et al. 1998; Olk et al. 2006) and increases the number of erroneous prosaccades to targets contralateral of the stimulation site (Terao et al. 1998).

The FEFs can control the outcome of oculomotor competition in several ways. First, the FEFs project to the intermediate layers of the superior colliculus (SC), an area in the midbrain generally assumed to be the location where bottom–up and top–down eye movement signals are integrated and mapped in a saccade map (Munoz et al. 2000; Trappenberg et al. 2001; Godijn and Theeuwes 2002). The FEFs contribute directly to saccade generation via the corticotectal tract (Segraves et al. 1987). Furthermore, there are multiple pathways between the FEFs and SC via the basal ganglia, some excitatory and others inhibitory (Munoz and Everling 2004). A recent study suggests that the pathway directly connecting the FEFs and SC is involved in the generation of pro- and antisaccades, while the pathways through the basal ganglia are involved in inhibiting or allowing the generation of prosaccades (de Weijer et al. 2010).

Here, oculomotor competition was investigated using an oculomotor capture task (Theeuwes and Kramer 1998; Godijn and Theeuwes 2002; Van der Stigchel et al. 2011). In this task, participants are presented with 6 circles positioned around a fixation point. After a brief interval, all but one of the circles change color. The participant is instructed to foveate the color singleton as fast as possible. In half of the trials, a task-irrelevant additional onset (distractor) is presented at the moment the circles change. Typically, in around 30% of the distractor trials, the participant's eyes are "captured" by the additional onset, even though this distractor is task-irrelevant (Theeuwes and Kramer 1998; Irwin et al. 2000; Godijn and Theeuwes 2002). An important difference between the antisaccade task and the oculomotor capture task is the role of the distracting onset: in the antisaccade task, this onset is task-relevant, because the participant needs to be aware of its location in order to suppress an automatic saccade toward it and generate a correct antisaccade instead. In the oculomotor capture task, however, the additional onset is task-irrelevant, since the participant does not need to know where it is in order to correctly perform the task (Theeuwes et al. 1999). Because the distractor does not need to be attended, the oculomotor capture task enables the investigation of the exact role of the FEFs in oculomotor competition when an irrelevant distractor is presented, as it constitutes a more direct contrast between automatic and volitional processes than the antisaccade task. Hence, neuronal processes underlying oculomotor inhibition instructed target saccade execution and automatic saccades can be properly distinguished, since the outcome of the competition can be derived from the saccade endpoint and its latency.

Single-pulse TMS was applied to study the role of the FEFs in the oculomotor capture task. First, participants performed an

eye movement task in a functional magnetic resonance imaging (fMRI) scanner to localize the FEFs. The individual FEF activation images enabled accurate stereotactic guidance of the TMS coil over the FEFs. TMS pulses were delivered over either the vertex, the left FEF, or the right FEF, at 25, 75, or 100 ms after target presentation, while participants performed the oculomotor capture task. The effect of TMS on the FEFs was expected to be reflected in the number of capture errors and in saccade latency. We expected effects for saccades to the hemifield contralateral to the FEF over which TMS was applied, based on earlier reports of contralateral saccade encoding in the monkey and human FEFs (Bruce et al. 1985; Beurze et al. 2009).

Materials and Methods

Participants

Twelve healthy subjects (1 female; average age 27, standard error [SE] 1) with normal or corrected-to-normal vision gave written informed consent and participated in 2 experiments. None of the participants had a history of mental or neurological disorders. Prior to the fMRI session (experiment 1), participants were screened for implanted metal objects. The research protocol was approved by the Medical Ethics Committee of Utrecht University (protocol 08-148).

Experiment 1

The goal of this fMRI experiment was to determine the location of the FEFs in each individual participant. A short but powerful fMRI paradigm (8 min) was used for localization.

Apparatus

The experiment was performed in a clinical 3-T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) with 8 receiver SENSE coils. Using Presentation software (Neurobehavioral Systems), stimuli were projected on a 1-m-wide screen that was placed at a distance of 2 m from the participants. Through a mirror mounted on the head coil, participants could view the stimuli.

Data Acquisition

For each participant, 960 functional T_2^*-weighted blood oxygen level–dependent (BOLD) volumes were acquired using a PRESTO-SENSE acquisition scheme (Neggers et al. 2008). Parameters were: time repetition [TR] = 21.75 ms; time echo [TE] = 32.4 ms; field-of-view [FOV] (ap, fh, rl) = 224 × 256 × 128 mm; flip angle = 10°; matrix: 64 × 64 × 32 slices; voxel size = 4 mm isotropic; 8-channel head coil; SENSE factor = 2 and 1.8 (in the left/right and anterior–posterior phase encoding directions, respectively). Acquisition time was 500 ms per volume. After the functional paradigm, a T_1-weighted anatomical scan was acquired (TE/TR 4.6/9.87 ms; flip angle 8°; FOV 224 × 160 × 168 mm; matrix 256 × 256; slice thickness 1 mm; slice gap 0; voxel size 0.875 × 0.875 × 1 mm). This anatomical scan was used for coregistration during analysis and for neuronavigation during placement of the TMS coil over the FEFs.

fMRI Paradigm

Participants had to make saccades during blocks of trials alternated with fixation epochs. Each trial started with a white circle (1° × 1° visual angle) at the center of a black screen. After 500 ms, the central white circle turned either red or blue. This colored circle was presented for 400 ms. When the circle turned blue, the participant had to make a prosaccade (toward the following peripheral target); a red circle indicated an antisaccade (directed opposite from the peripheral target with same eccentricity). Three hundred milliseconds after the colored circle cue disappeared, a peripheral target appeared on the left or right from the center for 800 ms at 3.8° or 14.8°. Depending on the type of trial, participants were instructed to make a saccade toward or away from this target as fast as possible. Each block consisted of 10 subsequent trials and took 20 s. After each block of trials, a fixation epoch followed (also lasting 20 s), during which participants were asked to fixate to a fixation cross at the center of the screen (1° × 1° of visual angle, line thickness 0.1°), presented on a black screen. The functional scanning session consisted of 12 saccade and 12 fixation blocks, amounting to a total of 8 min.

Data Analysis

The functional T_2^*-weighted volumes were analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). After realignment of the functional scans with the first image to correct for head movements, the images were coregistered to the T_1-weighted anatomical scan and resliced at 4 × 4 × 4 mm. Smoothing was applied to the resulting images using an 8-mm kernel full-width at half-maximum. The T_1-weighted scan was segmented to generate a gray matter probability map. This map was used to render a cortical 3D-image during neuronavigation. No normalization was applied to the anatomical scan, since the results from experiment 1 were used for the localization of each participant's individual FEFs for neural navigation, requiring undeformed images (normalization deforms MRI images). A 2-regressor general linear model was fitted to the functional images. The first regressor was a boxcar regressor (block length 20 s), convolved with the hemodynamic response function from SPM5, used to detect BOLD signal changes in voxels in oculomotor areas during saccade and fixation blocks. The second regressor was a constant baseline. A T-map was obtained, in which only voxels with regression coefficients significantly higher than zero ($P < 0.05$, corrected for multiple comparisons over the whole brain using a familywise error approach based on random field theory) were included. Previous studies have found that the resulting activation maps accurately localized the FEFs for each participant (Raemaekers et al. 2002; Neggers et al. 2005, 2007). The coordinates of the voxels in the left and right FEF with the highest values were stored and used for stereotactic guidance of the TMS coil in experiment 2.

Experiment 2

In this experiment, participants performed an oculomotor capture task while their eye movements were recorded and TMS pulses were delivered over the left and right FEF and the vertex at 25, 75, and 100 ms after target presentation.

Apparatus

The position of the right eye was monitored at 500 Hz using the video-based Eyelink II system (SR Research) with infrared video oculography. The infrared cameras were fixed to a head support. TMS was performed using a Neopulse stimulator (Neotonus, Atlanta, GA) with a focal squared figure-of-8 iron core TMS coil (Epstein and Davey 2002). A Pentium PC was used for stimulus presentation (custom software written in C++ using a Microsoft Visual Studio compiler) and the triggering of the TMS device through a pulse over the parallel port. A second PC, directly controlled by the aforementioned PC and software, was used to record eye positions. Visual stimuli were presented on a 19-inch Iiyama color monitor (refresh rate of 100 Hz, resolution of 1024 × 768, and an active screen size of 40 × 30 cm). The experiment was carried out in a dimly lit room. The participant was seated in front of a semisilvered mirror that slanted backward 45°.

The head of the participant was fixed against a head support (35 cm in front of the mirror) and a chin rest. Above the mirror, the CRT monitor was mounted facing down, which yielded an effective straight distance of 72 cm between the participant and the virtual image. This setup was used to maximize the distance between the monitor and the MiniBIRD magnetic position-tracking device that was used for neuronavigation, thereby reducing magnetic interference. The TMS coil was stereotactically guided over the FEFs of the participant using NEuroNAvigation (NENA, see http://www.neuralnavigator.com) software (Neggers et al. 2004) and the analyzed MRI data obtained in experiment 1.

Behavioral Paradigm

Participants completed 2 sessions, each consisting of 3 blocks of 192 trials. Each site of stimulation (left FEF, right FEF, and vertex) was stimulated once per session (hence the 3 blocks) and thus twice over the 2 sessions. Before every block, 24 practice trials were presented. The order of the blocks was counterbalanced over sessions and participants. Prior to every block, eye movement measurement was calibrated and validated using 9 randomly presented targets on a 3 × 3

grid. A trial was preceded by a drift correction, performed after 500 ms of stable fixation on a central white fixation plus sign (0.52° × 0.52°) on a black background. After a successful drift correction, the trial started. A central white fixation cross (0.52° × 0.52°) was presented on a black background. After 500 ms, 6 red circles (0.8° × 0.8°) appeared on a virtual circle (with a diameter of 10.5°) around the fixation cross. After 500–1250 ms, the fixation cross disappeared. Two hundred milliseconds later, 1 of 4 circles changed color into gray (red and gray were equiluminant at 10.4 cd). The circles at 15.00 or 21.00 h never changed color and thus were never targets (see Figure 1 for an illustration of the experimental design). Participants were required to make an eye movement to the color singleton within 1200 ms, after which the next drift correction started. In half of the trials (distractor trials), a rectangular gray distractor (0.7° × 0.7°) appeared in the visual field opposite from the target (either above or below the circles at 15.00 or 21.00 h), simultaneously with the target's color change. No feedback on the performance was provided during the experiment.

Because the colors used in the experiment were equiluminant, there was no luminance change at the target location when the target was presented. Therefore, search for the target was entirely endogenous, with no reflexive component that might activate a collicularly mediated visual grasp reflex driving the eyes to foveate a suddenly appearing peripheral stimulus (Machado and Rafal 2004). With respect to the distractor, there were 4 possible distractor locations. Although this limited number might have introduced a predictability of the possible distractor location, the distractor remained task-irrelevant: the participant did not need to know where the distractor was to correctly perform the task.

There were 3 timing conditions for TMS delivery: a single pulse was given either 25, 75, or 100 ms after the target's color change. A fourth set of trials was "catch" trials, in which no TMS pulse was delivered. This catch condition was included to prevent participants from waiting for the pulse before starting their saccade. These catch trials were interleaved randomly with TMS trials during each block. In total, there were 8 conditions per block (4 × 2): TIME (pulse times 25, 75, or 100 ms after target presentation, plus the aforementioned catch condition without a pulse) and CONDITION (no distractor and distractor). With 2 blocks of 192 trials per stimulation site, every condition effectively consisted of 48 trials.

Procedure

Before the experiment, the motor threshold (MT) was determined for each participant. MT was defined as the TMS device output intensity at which 5 of 10 TMS pulses over the cortical area involved in thumb movement evoked a visible twitch in the contralateral thumb (Schutter and van Honk 2006). By using this procedure, TMS output intensity during the experiment was adjusted for individual variability in conductivity of and excitability by the magnetic pulse. During the experiment, TMS pulses were delivered at 110% of the individual MT. After MT determination, the participant was asked to put on a tight-fitting cap on the head, on which the sites of stimulation were marked using image-guided neuronavigation. For fMRI-guided neuronavigation using the NeNa software version 2.0 (Brain Science Tools B.V., the Netherlands, http://www.neuralnavigator.com), 8 anatomical landmarks on the head of the participant were measured (tip of the nose and nose bridge, the inner and outer points of both eye lids, and the upper adherence of the ears) with a MiniBIRD magnetic position tracker. Corresponding points were marked on a computer-generated rendering of the participant's skin (the T_1-weighted anatomical scan was used for this rendering; see Fig. 2). A cortical rendering was loaded and visualized in the software using the gray matter segmented image obtained in experiment 1, on which the FEF activation map was superimposed. After alignment of the MRI space markers placed on the skin rendering and the real landmarks as measured on the subjects face, the digitizer pen of the MiniBIRD tracker could be rendered on the screen in real time when it was moved over the participant's head.

This allowed for localization of the points on the participant's scalp directly overlying the points within the left and right FEF at which peak activation was found in the fMRI task (see Figure 3 for the activation maps of all participants). When a medial and lateral activation cluster was observed in the FEFs, as reported by several recent studies (Curtis and Connolly 2008; Neggers et al. 2012), we chose the medial activation: human medial FEFs have recently been shown to be involved in generating voluntary saccades (Amiez et al. 2006; Neggers et al. 2012). The vertex was defined as the point on the sagittal midline right between the left and right FEF and the inferior parietal sulcus. These points were marked on the head cap the participants were wearing. For more details on the procedure of TMS coil placement, see Neggers et al. (2004). After every block, the position of the coil on the participant's head was checked and corrected if necessary.

Data Analysis

For each trial, the latency of the first saccade in each trial was computed as the difference between eye movement onset and target array presentation. Trials in which this latency was shorter than 80 ms were excluded from analysis. Trials were discarded when the interval between target presentation and arrival of the saccade within 3° of the target was longer than 500 ms or was more than outside 2.5 standard deviations from the mean. Only trials in which the target was fixated within 2 saccades were included. Furthermore, when the saccade started more than 3° visual angle away from the fixation point or had an end position that was further from 1 of the 6 circles than 3° of the visual angle, the trial was excluded. A distractor trial was classified as a capture trial when the first saccade landed within 3° of the distractor before a second saccade was made to the target.

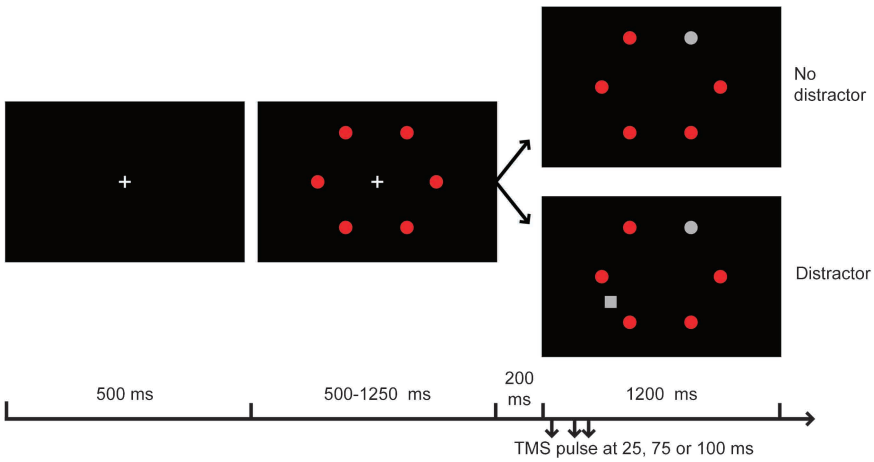

Figure 1. A schematic of the 2 conditions in the oculomotor capture task. In each trial, 1 of 4 circles on an imaginary circle around fixation changed color (the circles at 15.00 and 21.00 h never changed color). In half of the trials, a gray rectangular distractor was presented above or below the circles at 15.00 and 21.00 h in the visual field opposite to the target.

Most accounts in the literature show a contralateral effect of TMS over the FEFs (Terao et al. 1998; Olk et al. 2006; Neggers et al. 2007; Van Ettinger-Veenstra et al. 2009), which can be expected based on the contralateral coding of oculomotor space for saccades that is well known to exist in monkey FEFs (Bruce et al. 1985) and humans (Beurze et al. 2009). We therefore pooled trials with contralateral targets and trials with ipsilateral targets with respect to the stimulated FEF. That is, data from trials with a target in the right visual field during left-FEF stimulation were pooled in the "contralateral" condition with data from trials with targets in the left visual field during right-FEF stimulation, while pooling in the "ipsilateral" condition was performed vice versa. Data from trials in the vertex condition (leftward and rightward) were also pooled. Trials in which a distractor was presented were divided into a group of trials that went to the distractor (capture trials) and a group of trials that did not (no-capture trials). For each subject, the average saccade latency was computed for all 27 resulting conditions (3 × 3 × 3): site of stimulation (SITE: ipsilateral FEF, contralateral FEF, and vertex), TIME (pulse times 25, 75, and 100 ms after target presentation), and SACCADE TYPE (no-distractor trials, no-capture distractor trials, and capture distractor trials). Furthermore, the percentage of capture trials was computed for the 9 distractor conditions (3 × 3: TIME and SITE).

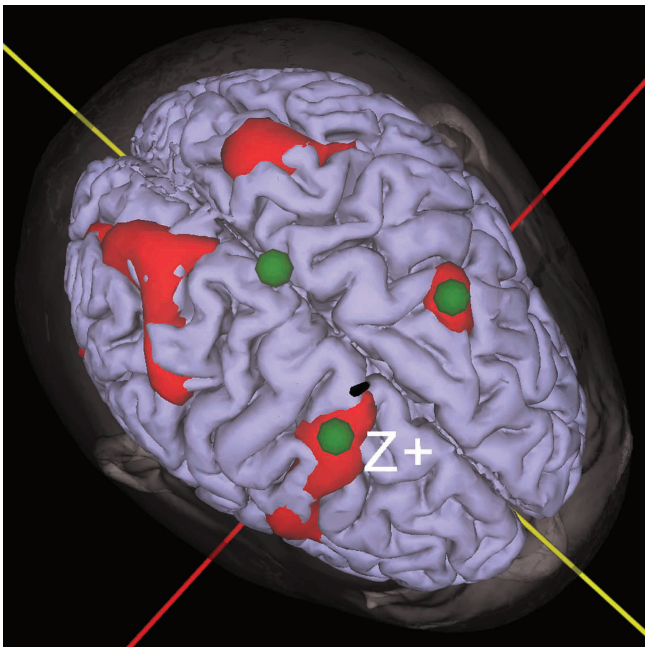

Figure 2. A 3D rendering of the skin and segmented gray matter surface for one of the participants (see Neggers et al. 2004 and http://www.neuralnavigator.com) from the neural navigator software. fMRI activation during the localizer task is shown superimposed in red. The FEFs and the intraparietal sulcus can clearly be distinguished. The green targets demarcate the sites of stimulation: left FEF, right FEF, and vertex.

Results

Experiment 2

Excluded Trials

On average, 26.0% of the trials were discarded. In 22.2% of the trials, the eye movements did not satisfy the end position criteria; in 3.8%, the saccade fell outside the latency criteria. The percentages of included trials did not differ significantly between stimulation sites (M 78.5%, SE 3.2% of vertex trials; 71.2%, SE 3.6% of ipsilateral trials; and 72.2%, SE 3.1% of contralateral trials) ($F_{2,33}$ = 1.415; P = 0.257).

Functional Differences between the Left and the Right FEF.

As described above, the data from the 2 TMS sessions of the same region (left or right FEF or vertex) were pooled before analysis. Because there have been some reports in the literature of functional differences between the left and the right FEF (Petit et al. 2009; Szczepanski et al. 2010), we investigated potential functional differences between the FEFs on saccade latency by performing a repeated measures analysis with factors TIME, STIMFEF (stimulated FEF, left or right), LATERALITY (of target with respect to stimulated FEF: ipsi- or contralateral), and SACCADE TYPE (no-distractor, distractor-to-target, or distractor-

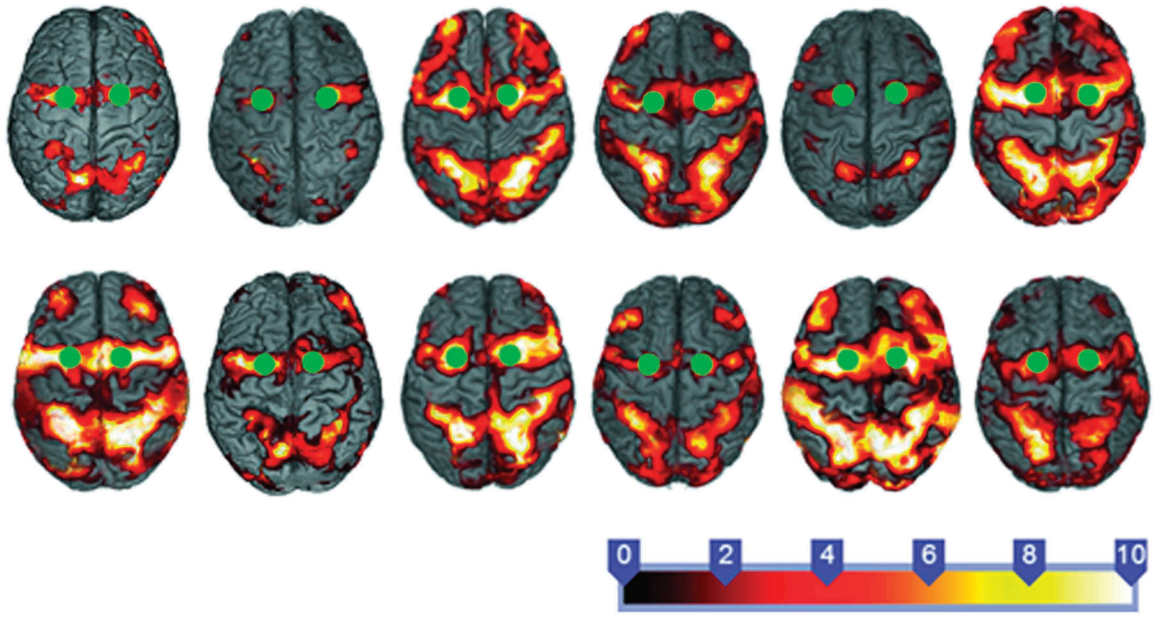

Figure 3. The activation maps for all 12 participants. For this figure, the MRI scans and activation maps were normalized to Montreal Neurological Institute space. In all participants, the FEFs are clearly activated.

to-distractor). The factor STIMFEF did not show a significant main effect ($F_{1,7}$ = 0.097; P = 0.765). None of the interactions between STIMFEF and the other factors were significant. Another repeated measures analysis was performed to explore functional differences between the FEFs on the percentage of capture trials, including factors TIME, STIMFEF, and LATERALITY. There was no significant main effect of STIMFEF on performance ($F_{1,11}$ = 0.386; P = 0.547). The interactions of STIMFEF with other factors were not significant. The results from these analyses indicate that there were no functional differences between the two FEFs on the behavioral measures.

TMS Effect on Performance

For distractor trial conditions, the percentage of trials in which a saccade was made to the distractor was computed. The percentages were subjected to a repeated measures analysis of variance, including factors TIME and SITE (ipsi- or contralateral FEF stimulation, vertex).

This analysis yielded a significant effect of TIME ($F_{1.359,14.951}$ = 6.801; P = 0.014). Contrasts revealed that this effect was linear ($F_{1,11}$ = 10.148; P = 0.009): the percentage of capture trials was significantly higher for the 25 ms pulse timing (M 34.7%, SE 4.5%) than for 75 ms (M 31.6%, SE 3.7%), which was in turn significantly higher than the 100 ms pulse timing (M 26.0%, SE 3.3%).

The factor SITE yielded a significant effect ($F_{2,22}$ = 4.987; P = 0.016). Contrasts showed that contralateral trials had a lower percentage of capture trials (saccades to the distractor, 24.7%, SE 2.8%) than ipsilateral trials (34.6%, SE 5.0%) and vertex trials (33.0%, SE 4.2%) ($F_{1,11}$ = 7.014; P = 0.023 and $F_{1,11}$ = 5.186; P = 0.044, respectively). Vertex and ipsilateral trials did not differ significantly ($F_{1,11}$ = 0.374; P = 0.553). Thus, when the target was presented in the visual field contralateral to FEF stimulation and the distractor was in the ipsilateral visual field, FEF TMS decreased the percentage of capture trials compared with the inverse situation (target in visual field ipsilateral to stimulation, distractor contralateral) and the vertex condition. This effect is shown in Figure 4. The interaction TIME × SITE was not significant ($F_{4,44}$ = 1.031; P = 0.402).

In this task, the distractor was always presented on 1 of 2 locations in the visual hemifield opposite to the target. These distractor locations were not equidistant to the target (the "near" distractor location was 14.87° away from the target, the "far" location 20.32°). To test whether the distance between the distractor and the target had an influence on the percentage of capture trials, we computed the percentage of capture trials for trials in which the distractor was near versus far, for the vertex, ipsilateral, and contralateral FEF conditions. A repeated measures analysis with factors SITE (vertex, ipsilateral, and contralateral FEF) and DISTRACTOR DISTANCE (near or far) was performed. There was a significant main effect of SITE ($F_{1.214,13.356}$ = 28.018; P < 0.001), similar to the effect discussed above. More interestingly, there was a significant main effect of distractor distance ($F_{1,11}$ = 14.869; P = 0.003): there were significantly more capture trials when the distractor was near (M 44.0%, SE 4.9%) compared with when the distractor location was far from the target (M 37.1%, SE 4.3%). This effect is consistent with work by Theeuwes and Kramer (1998), who showed that the occurrence of oculomotor capture increases when distractors are closer to the target. There was no significant interaction effect, revealing that the site of stimulation did not modulate the influence of the distance between target and distractor.

TMS Effect on Saccade Latency

Based on previous literature (Godijn and Theeuwes 2002; Mulckhuyse et al. 2008), shorter latencies were expected for trials in which the eyes were captured by a distractor than for the trials in which a correct eye movement was executed toward the target. Therefore, trials in which a distractor was presented were divided into to-distractor/capture trials and to-target/no-capture trials. A repeated measures analysis was performed with factors TIME, SITE, and SACCADE TYPE (no-distractor trials, no-capture/to target distractor trials, and capture distractor trials). The results are illustrated in Figure 5.

There was a significant main effect of SACCADE TYPE ($F_{1.057,11.626}$ = 36.189; P < 0.001, Greenhouse–Geisser

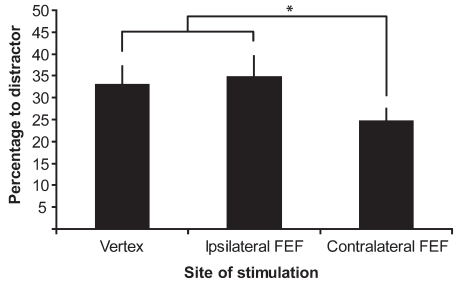

Figure 4. Average percentage of trials in which saccades went to the distractor for the 3 sites of stimulation. Data were averaged across pulse timings. Note that the "Site of stimulation" refers to the hemifield in which the target was located with respect to the stimulated hemisphere; that is, contralateral implies a target contralateral and distractor ipsilateral with respect to the stimulated FEF and ipsilateral implies a target ipsilateral with respect to the stimulated FEF. The error bars represent standard errors of the mean.

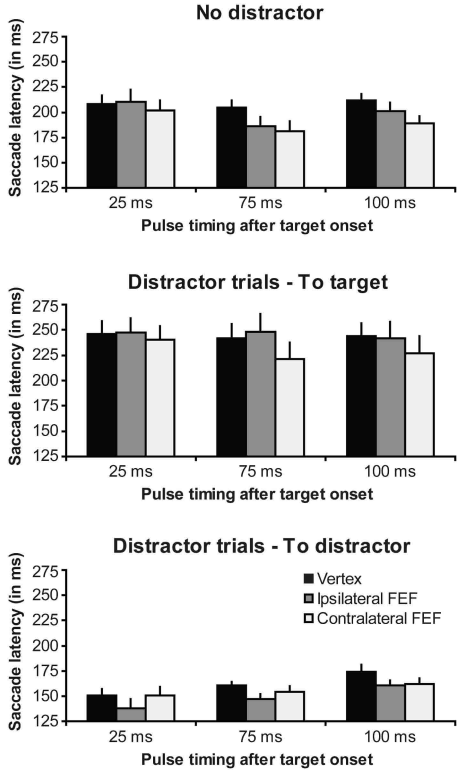

Figure 5. Average saccade latency per stimulation site for the 3 pulse timings, split for saccade type. The error bars represent standard errors of the mean.

corrected). Contrasts revealed that capture saccades in distractor trials (*M* 155 ms, SE 4 ms) had significantly shorter latencies than saccades in no-distractor (*M* 199 ms, SE 7 ms, [$F_{1,11}$ = 58.028; P < 0.001]) and no-capture saccades in distractor trials (*M* 240 ms, SE 13, [$F_{1,11}$ = 37.764; P < 0.001]). Furthermore, latencies of no-capture saccades in distractor trials were significantly longer than those of saccades in no-distractor trials ($F_{1,11}$ = 22.161; P = 0.001).

There was no main effect of TIME ($F_{1.264,13.905}$ = 1.517; P = 0.246, Greenhouse–Geisser corrected), indicating that the timing of the TMS pulses did not influence saccade latencies in general. There was a main effect of SITE ($F_{2,22}$ = 7.224; P = 0.004): contralateral FEF stimulation trials (*M* 192 ms, SE 7 ms) on average had significantly shorter latencies than vertex stimulation trials (*M* 205 ms, SE 7 ms; [$F_{1,11}$ = 12.283; P = 0.005]). The latency differences between contralateral and ipsilateral FEF stimulation trials (*M* 198 ms, SE 8 ms) and ipsilateral and vertex trials were not significant ([$F_{1,11}$ = 3.855; P = 0.075] and [$F_{1,11}$ = 4.060; P = 0.069], respectively).

There was a significant interaction between TIME and SACCADE TYPE ($F_{2.371,26.078}$ = 4.182; P = 0.021, Greenhouse–Geisser corrected): while the latencies of capture saccades in distractor trials linearly became longer with increased time interval between target presentation and pulse, latencies of saccades in no-distractor trials and no-capture saccades in distractor trials stayed level between pulse time conditions (linear contrasts: [$F_{1,11}$ = 6.244; P = 0.030] and [$F_{1,11}$ = 8.653; P = 0.013], respectively). This effect is consistent with the observed higher percentage of capture trials for the early pulse times: the short latencies resulted in an increased number of (fast) capture trials in these conditions.

There was a significant interaction between SITE and SACCADE TYPE ($F_{4,44}$ = 3.357; P = 0.018): while for distractor trials in which the eye went to the distractor, saccade latencies were longer for contralateral than for ipsilateral FEF stimulation trials, the opposite (shorter latencies for contra than for ipsi FEF trials) was true for no-distractor trials or distractor-no capture trials ([$F_{1,11}$ = 9.135; P = 0.012] and [$F_{1,11}$ = 7.663; P = 0.018], respectively). In other words, in trials in which the target was presented contralateral to the stimulated FEF and a (capture) saccade was made to an ipsilateral distractor, the saccade latency was longer than for capture trials in which the target was presented ipsilateral (and the distractor contralateral) to stimulation. In contrast, the opposite effect was observed in distractor trials in which the eye movement was initiated toward the target and in no-distractor trials: saccade latencies were shorter when the target (to which the eye movement was made) was contralateral to the stimulated site compared with when the target was presented ipsilateral to stimulated site. Importantly, the application of TMS on the FEFs thus facilitated contralateral saccades, irrespective of whether they were initiated toward the target or the distractor.

There was no significant interaction between SITE and TIME ($F_{4,44}$ = 1.814; P = 0.143). The 3-way interaction between SITE × TIME × SACCADE TYPE was not significant ($F_{1.563,17.190}$ = 0.684; P = 0.483). As can be seen in Figure 5, however, SACCADE TYPE seemed to differ subtly in their interactions with the other factors. For completeness of the analyses, we decided to look further into the latency differences for the 3 different saccade types. Repeated measures analyses (with factors TIME and SITE) were performed for no-distractor trials, no-capture/to target distractor trials and capture distractor trials separately:

No-distractor trials. For no-distractor trials, there was a significant main effect of SITE ($F_{2,22}$ = 7.448; P = 0.003): saccades in contralateral FEF stimulation trials had shorter latencies (*M* 191 ms, SE 7 ms) than saccades in ipsilateral (*M* 199 ms, SE 9 ms; [$F_{1,11}$ = 5.200; P = 0.044]) and vertex trials (*M* 208 ms, SE 7 ms; [$F_{1,11}$ = 10.765; P = 0.007]). The saccades in ipsilateral and vertex trials did not differ significantly in latency ($F_{1,11}$ = 4.113; P = 0.067). No significant main effect of TIME was found ($F_{1.050,11.551}$ = 2.715; P = 0.126, Greenhouse–Geisser corrected). There was a significant interaction between TIME × SITE ($F_{4,44}$ = 3.606; P = 0.013): latencies of saccades in vertex and ipsilateral FEF stimulation trials did not differ significantly in the 25 ms stimulation condition (T_{11} = –0.45; P = 0.661), but in the 75 ms condition, latencies of saccades in ipsilateral trials were significantly shorter than those of vertex trials (T_{11} = 3.672; P = 0.004) (contrast statistic: [$F_{1,11}$ = 12.785; P = 0.004]). The other contrasts were not significant. The main effect of SITE, however, indicates that saccades in contralateral FEF stimulation trials were generally faster than ipsilateral and vertex trials for the no-distractor trials.

Distractor trials—to target. For distractor trials in which saccades went to the target, a significant main effect was found for SITE ($F_{2,22}$ = 4.008; P = 0.033), which was driven by shorter latencies for saccades in the contralateral FEF stimulation condition (*M* 229 ms, SE 15 ms) than for ipsilateral (*M* 246 ms, SE 14 ms; [$F_{1,11}$ = 5.721; P = 0.036]) and vertex at the trend level (*M* 244 ms, SE 13 ms; [$F_{1,11}$ = 4.755; P = 0.052]) conditions. There was no significant main effect of TIME ($F_{1.377,15.144}$ = 0.854; P = 0.405). The interaction between TIME and SITE was not significant ($F_{1.284,14.122}$ = 0.559; P = 0.509, Greenhouse–Geisser corrected). For distractor trials in which an eye movement was made to the target, shorter saccade latencies were observed when the target was presented contralateral than when the target was ipsilateral to FEF stimulation.

Distractor Trials—to Distractor. For distractor trials in which saccades went to the distractor, there was a significant main effect of TIME ($F_{2,22}$ = 6.109; P = 0.008): latencies of saccades in trials where a TMS pulse was administered at 100 ms after target onset (*M* 166 ms, SE 5 ms) were significantly longer than those in the 25 ms (*M* 146 ms, SE 7 ms; [$F_{1,11}$ = 8.909; P = 0.012]) and the 75 ms (*M* 154 ms, SE 4 ms; [$F(1, 11)$ = 8.729; P = 0.013]) stimulation conditions. Furthermore, a significant main effect of SITE was obtained ($F_{2,22}$ = 4.423; P = 0.024). Contrasts showed that this effect was driven by a significant latency difference between saccades in the vertex (*M* 162 ms, SE 5 ms) and ipsilateral FEF (i.e., stimulation ipsilateral to the target and contralateral to the distractor, *M* 149 ms, SE 6 ms) stimulation conditions ($F_{1,11}$ = 6.697; P = 0.025). Other contrasts were not significant. There was no significant interaction effect between TIME and SITE ($F_{4,44}$ = 1.139; P = 0.351). These results confirm our findings that saccades to contralateral distractors were accelerated by TMS on the FEFs compared with vertex TMS saccades.

TMS Effect on Target Saccade Endpoint Distributions

Previous research has shown that the saccade endpoint can be influenced by the presentation of a distractor in close proximity of the target (Van der Stigchel and Nijboer 2011). Therefore, we investigated whether the endpoint of a saccade toward the target was influenced by FEF TMS. To this end, the

angle of the endpoint of any first saccade that went toward the target was computed. This angle was defined as the angle between the horizontal meridian and the vector between the fixation point and the saccade endpoint. The obtained angle was then subtracted from the angle between the horizontal meridian and the target location to compute the saccade endpoint with respect to the target. For each target location, a repeated measures analysis was performed with factors SITE (vertex, ipsilateral, and contralateral stimulation) and CONDITION (no distractor or distractor). In none of the analyses, effects of CONDITION were found ([$F_{1,11}$ = 0.519; P = 0.486], [$F_{1,11}$ = 0.953; P = 0.350], [$F_{1,11}$ = 0.374; P = 0.553], [$F_{1,11}$ = 2.672; P = 0.130] for the 4 target locations). There were no effects of SITE or interaction effects. Furthermore, we performed repeated measures analyses for distractor trials with factors SITE and DISTRACTOR DISTANCE (near or far, also see TMS effect on performance) for each target location. No significant effects for DISTANCE were found ([$F_{1,10}$ = 0.051; P = 0.825], [$F_{1,9}$ = 0.34; P = 0.858], [$F_{1,11}$ = 0.044; P = 0.838], [$F_{1,10}$ = 2.091; P = 0.179] for the 4 target locations), and there also were no significant main effects of SITE or interaction effects.

There were thus no differences between FEF (ipsi- or contralateral) stimulation and vertex stimulation on target saccade endpoints, regardless of whether the distractor was near or far to the target. The absence of such an effect might be explained by the distance between the target and the distractor. Previous research has indicated that the saccade averaging generally occurs when target and distractor are presented in a zone of 20° in polar coordinates (Van der Stigchel and Nijboer 2011). Here, the minimal distance between target and distractor was 72° in polar coordinates.

Discussion

In the current study, we systematically investigated the role of the FEFs in oculomotor competition when a task-irrelevant distractor is present. A single TMS pulse was applied at several intervals after target presentation over left FEF, right FEF, or vertex during an oculomotor capture task. To maximize the precision of the stimulation, the TMS coil was stereotactically guided by MRI scans and fMRI activation maps. Although previous studies have found functional differences between the left and the right FEF (Petit et al. 2009; Szczepanski et al. 2010), these differences were not present in our study (in line with Terao et al. 1998; Neggers et al. 2007, 2012; Beurze et al. 2009; Van Ettinger-Veenstra et al. 2009). Therefore, we pooled data from both FEFs and analyzed the data in terms of the location of the target with respect to the side of stimulation (contralateral or ipsilateral).

Models of eye movement control have proposed that the selection of a saccade target is the result of the competitive integration of higher-order and top–down information on a common saccade map (Trappenberg et al. 2001; Godijn and Theeuwes 2002). In these models, the saccade is initiated to the location with the highest activity. In capture trials, it is assumed that the location of the distractor is associated with the highest activity in the saccade map. In contrast, when the saccade is directed to the target, the activity at the distractor location is supposed to be successfully suppressed and the location of the target sufficiently enhanced. This notion is supported by the fact that within the monkey FEFs, over time the target for a saccade is enhanced with respect to neuronal representations of distracting items (Schall et al. 1995). In the present study, we observed that when a distractor was presented, eye movements were frequently erroneously directed toward the distractor before being directed to the target. Results showed that TMS over the FEFs decreased the percentage of these capture trials when the target was presented in the visual field contralateral to the stimulated hemisphere (compared with vertex stimulation). When the target was presented in the visual field ipsilateral to the stimulated hemisphere, no difference in capture trials with vertex stimulation was observed. The distractor was always presented in the visual field opposite to the target, so this latter condition refers to trials in which the distractor was presented contralateral to the stimulated hemisphere. Because it is known that the FEFs (in monkeys as well as in humans) code the oculomotor space for contralateral saccades (Bruce et al. 1985; Kastner et al. 2007; Beurze et al. 2009), our results indicate that TMS over the FEFs influences the target representation and not the representation of the distractor. A purely perceptual explanation of this effect can be excluded, because it would imply that both the target and the distractor representations are enhanced in the contralateral hemifield, which would have resulted in an increased number of capture trials for contralateral distractors (ipsilateral targets) with respect to vertex stimulation. The present study therefore shows that contralateral TMS enhances the selection of the target in the face of strong oculomotor competition (e.g., when a competing ipsilateral distractor is present).

Results of neurophysiological recordings have already pointed to the involvement of the FEFs in oculomotor competition (Bichot and Schall 2002). Initially, neurons in the FEFs respond to any stimulus in their receptive field, but over time (around 100–150 ms after stimulus presentation) potential targets are enhanced, while identified distractors are inhibited (Bichot and Schall 2002). Our results are congruent with that notion: applying TMS to the FEFs enhances contralateral targets, most likely through the excitatory direct pathway to the ipsilateral SC via the basal ganglia (see also Meeter et al. 2010) or the direct connections between the FEFs and the SC bypassing the basal ganglia. It could be speculated that the effect of TMS in our study is excitatory and that the inhibition of a distractor is not influenced by the application of a single pulse of TMS. Probably, excitatory input from the FEFs to the SC indicates where the instructed saccade target is located, and the SC mainly integrates that signal with other bottom–up signals it receives from the oculomotor or visual areas. In our experiment, we could have boosted this descending target-encoding signal from the FEFs to the SC, favoring a saccade to the target location over a saccade to the distractor. That would imply that the actual competition between automatic visually guided saccades and instructed target saccades takes places within the SC itself, and not the FEFs, as has also been suggested by others (Munoz et al. 2000; Trappenberg et al. 2001; Godijn and Theeuwes 2002).

Previous studies on the influence of TMS on the FEFs have revealed an important role for the FEFs in the deployment of visual attention in space (Grosbras and Paus 2002; Muggleton et al. 2003; Neggers et al. 2007; Van Ettinger-Veenstra et al. 2009). For instance, Muggleton et al. (2003) showed that the FEFs are critical for the visual selection of a target in both a conjunction and a feature search task. These findings are consistent with the current observation that TMS facilitated

a saccade toward a target element in the face of oculomotor competition. Indeed, many researchers have argued for a strong overlap between the oculomotor and the attentional system (Rizzolatti 1978; Deubel and Schneider 1996; Van der Stigchel and Theeuwes 2007). In line with experimental work revealing that the FEFs are responsible for the coupling between shifts of visuospatial attention and eye movements (Neggers et al. 2007; Van Ettinger-Veenstra et al. 2009), the current results can therefore also be explained in terms of an enhancement of attentional processes.

The analyses of the saccade latencies revealed an additional role of the FEFs in oculomotor competition. TMS over the FEFs sped up the initiation of an eye movement to the contralateral visual field, irrespective of whether the saccade was directed to the target or the distractor. Saccade latencies were shorter when TMS was applied to the contralateral hemisphere for saccades to the target in both the no-distractor and the distractor trials, but also for capture trials. This faster initiation of eye movements was thus observed for both the target and the distractor representations, in contrast to the results of the percentage of capture saccades. The faster initiation of eye movements to the contralateral visual field is in line with previous studies (Van Ettinger-Veenstra et al. 2009). Note that most studies investigating effects of TMS on the FEFs on saccade latencies observed delays of prosaccades (Priori et al. 1993) and antisaccades (Terao et al. 1998). However, the aforementioned studies administered TMS much later than was done in our study, that is, shortly before saccade onset. Van Ettinger-Veenstra et al. (2009) administered TMS on the FEFs much earlier during saccade preparation, around the same time we did, and also observed decreases of saccade latency.

It has to be noted that the lower percentage of capture saccades cannot be explained by the influence of TMS on saccade latencies. There is a strong relation between saccade latency and percentage of saccades to the distractor: capture saccades are observed most frequently for saccades with a short latency (Mulckhuyse et al. 2008). Because saccade latencies to the target became shorter after TMS was applied to the contralateral hemisphere, this should have resulted in more capture saccades. In contrast, FEF TMS decreased the percentage of capture saccades when the target was presented in the contralateral visual field.

The exact timing of the TMS pulse did not differently influence the enhancement of target selection. TMS pulses were delivered at 25, 75, or 100 ms after target presentation. This indicates that the FEFs enhance target selection throughout this time period. Because the different pulse times were relatively close in time, it might very well be that a different timing of the pulses would have resulted in dissociations between the different pulse times. Previous studies have for instance presented pulses before the target was presented (Grosbras and Paus 2002; Van Ettinger-Veenstra et al. 2009), possibly influencing different mechanisms during oculomotor selection.

Interestingly, previous studies found contralateral (Terao et al. 1998) as well as ipsilateral (Muri et al. 1991; Terao et al. 1998; Olk et al. 2006) effects of FEF stimulation on antisaccade task measures, whereas only contralateral effects were observed in the current study. These differences might be explained by differences between the 2 tasks. In the antisaccade task, the to-be-inhibited onset needs to be selected and inhibited in order to make a correct antisaccade. For eye movements both to the visual hemifield ipsilateral and contralateral to stimulation, automatic and volitional processes are therefore needed to perform the task. In contrast, in the oculomotor capture task, the onset does not need to be attended in order to successfully perform the task. The oculomotor capture task thus allows for a direct contrast between automatic (to distractor) and volitional (to target) processes, whereas in the antisaccade task, these processes cannot be separated. On the basis of the present results, we argue that the previous findings in the antisaccade task can be explained by the double status of the onset: the representation of a contralateral onset is enhanced by FEF TMS (because it is task-relevant), leading to an increased number of erroneous prosaccades to that onset (Terao et al. 1998) and delayed latencies for antisaccades directed ipsilaterally (Muri et al. 1991; Terao et al. 1998; Olk et al. 2006).

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Notes

Conflict of Interest : None declared.

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