fMRI-Guided TMS on Cortical Eye Fields: The Frontal But Not Intraparietal Eye Fields Regulate the Coupling Between Visuospatial Attention and Eye Movements

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Van Ettinger-Veenstra HM, Huijbers W, Guttingel TP, Vink M, Kenemans JL, Neggerson SFW. fMRI-guided TMS on cortical eye fields: the frontal but not intraparietal eye fields regulate the coupling between visuospatial attention and eye movements. J Neurophysiol 102: 3469–3480, 2009. First published October 7, 2009; doi:10.1152/jn.00350.2009. It is well known that parts of a visual scene are prioritized for visual processing, depending on the current situation. How the CNS moves this focus of attention across the visual image is largely unknown, although there is substantial evidence that preparation of an action is a key factor. Our results support the view that direct corticocortical feedback connections from frontal oculomotor areas to the visual cortex are responsible for the coupling between eye movements and shifts of visuospatial attention. Functional magnetic resonance imaging (fMRI)–guided transcranial magnetic stimulation (TMS) was applied to the frontal eye fields (FEFs) and intraparietal sulcus (IPS). A single pulse was delivered 60, 30, or 0 ms before a discrimination target was presented at, or next to, the target of a saccade in preparation. Results showed that the known enhancement of discrimination performance specific to locations to which eye movements are being prepared was enhanced by early TMS on the FEF contralateral to eye movement direction, whereas TMS on the IPS resulted in a general performance increase. The current findings indicate that the FEF affects selective visual processing within the visual cortex itself through direct feedback projections.

INTRODUCTION

By using selective visual processing, the human brain can filter relevant parts in a scene from a wealth of distracting information. Such selectivity is commonly referred to as visuospatial attention. Previous psychophysical studies demonstrated that visuospatial attention is tightly coupled to the preparation of saccadic eye movements; objects are perceived better when they are the target of a saccade in preparation (Deubel and Schneider 1996; Godijn and Theeuwes 2003; Hoffmann and Subramaniam 1994; Neggerson et al. 2007). Although it should be noted that saccade preparation and covert attentional shifts can be dissociated under the right circumstances (Juan et al. 2004, 2008), there is consensus that saccade preparation is an important regulatory factor in covert attentional shifts.

This coupling has been explained in broad terms by the premotor theory of attention (Rizzolatti et al. 1987), stating that shifting attention is related to preparing a saccade. Similar activity patterns during saccades and covert visual attention shifts in the ventral intraparietal sulcus (IPS) and the frontal eye fields (FEFs) support that notion (Corbetta and Shulman 1998; Moore and Fallah 2001; Van der Lubbe et al. 2005). The FEF and IPS are part of the oculomotor control pathway conveying signals from the visual cortex to the midbrain (Munoz et al. 2004) and finally the brain stem (Sparks 2002).

More specifically, recent studies suggest that the FEF controls selective visual processing through reverse projections to the visual cortex. Moore and Armstrong (2003) demonstrated that electrostimulation of monkey FEF sites elicited activity in V4 neurons with matching receptive fields. Super and colleagues (2004) reported enhanced activation in monkey V2 neurons 100–200 ms before saccades into the receptive field. Interestingly, FEF electrical stimulation enhances luminance discrimination performance (Moore and Fallah 2001, 2004), indicating that FEF projections indeed affect visual processing. Furthermore, Ekstrom and colleagues (2008) demonstrated that electrical stimulation of monkey FEF modulated activity as measured by functional magnetic resonance imaging (fMRI) in early visual areas, but only when visual stimulation was present. These findings inspired several attempts to demonstrate the existence of similar networks in human subjects, mostly using noninvasive single-pulse transcranial magnetic stimulation (TMS) of the FEF and/or the IPS. TMS on the FEF or IPS during functional magnetic resonance imaging (fMRI) evokes occipital activation (Ruff et al. 2006, 2008), albeit of a different nature for each stimulation site. Importantly, the latter studies also reported an increase in visual-discrimination performance along with the FEF–TMS-evoked occipital enhancements. TMS on the human FEF alters ipsilateral occipital electroencephalographic (EEG) signals (Taylor et al. 2006) and enhances visual awareness (Grosbras and Paus 2003; O’Shea et al. 2004; Ruff et al. 2006). Furthermore, TMS on the FEF lowers the threshold of a second TMS pulse on V4 needed for eliciting phosphene, vivid TMS-evoked visual illusions (Silvanto et al. 2006). It can be concluded that a single pulse of TMS on the FEF may induce a primary processing area needed for visual processing, probably through connections to the visual cortex.

The reported reverse projections from the FEF back to the visual cortex can also explain the strong coupling between
saccade programming and visual processing, as demonstrated by Deubel and Schneider (1996), above and beyond the mere enhancement of visual cortical processing by signals from the FEF. That is, when saccade preparatory activation in the FEF, as reported not only for nonhuman (Schall et al. 1995b) but also for human primates (Van der Lubbe et al. 2006), is relayed to the visual cortex zones with a matching retinotopic topography, this could explain why perception is improved at locations of upcoming saccades. We could recently show using EEG and source localization that during the same paradigm as adopted by Deubel and Schneider (1996), activation in the FEF contralateral to the saccade in preparation preceded similarly lateralized activation in the occipital lobe, well before saccade execution (Gutteling et al. 2009). The temporal order of cortical activation in the latter study implicates a causal relationship between both areas during saccade preparation, which was further strengthened by a study adopting TMS on the FEF using the exact same behavioral paradigm (Neggers et al. 2007). The latter study administered a brief train of three TMS pulses onto the FEF just prior to presentation of a discrimination target (DT) at or next to the location to which a saccade was being prepared. TMS on the FEF contralateral to saccade direction disrupted the known coupling between saccade preparation and target discrimination. This was interpreted as TMS disturbing the modulating effect of signals from the FEF to the visual cortex. However, it could not be fully ruled out that the discrimination performance decreases after TMS on the FEF resulted from neural interference with visual processing in the FEF itself. That is, the effects of the TMS pulse train in the FEF might have outlasted the actual time of stimulation and would thus be able to disturb incoming visual information within the FEF. Furthermore, the pathway through which the FEF modulates the visual cortex is not known. The IPS might be included as an intermediate in the FEF projections to the visual cortex, or the connections could be direct, bypassing the IPS. Ruff and colleagues (2008) also demonstrated that the human IPS is connected to the visual cortex, even though TMS on the IPS yielded different effects compared with TMS onto the FEF.

The present study was performed to clarify the temporal characteristics of FEF involvement in visual attention shifts, as well as the possible pathways by which the FEF might exert its influence over the visual cortex. To establish the critical time window before saccade execution in which the human FEFs have an influence over visual processing, the left and right FEF and IPS were stimulated with a single TMS pulse at variable times during saccade preparation, using fMRI-guided stereotaxy. If frontooccipital connections are indeed responsible for attentional modulations, TMS signals from the FEF and incoming visual signals from the retina should arrive in the visual cortex around the same time, to result in a maximal influence of TMS with visual processing. Therefore the optimal time from TMS stimulation to the moment of target presentation (which we defined as a moment halfway to DT presentation; see METHODS) should equal the electrical signal transmission from the FEF to the visual cortex (~100 ms; see following text) minus the transmission time from the retina to the visual cortex (~66 ms), yielding about 34 ms. The average visual latency for the primary visual cortex (V1) of macaque is about 66 ms (Schmolesky et al. 1998). This latency is compatible with the time range of the first visual response in human V1, as confirmed using concurrent EEG and fMRI (Di Russo et al. 2002). We roughly estimated the FEF→visual cortex conduction time at about 100 ms based on the following two studies. First, monkey FEF presaccadic preparatory activity is reported to start about 50 to 60 ms after stimulus presentation in a study also using multiple-target configurations (Thompson et al. 2005). The discussed presaccadic activity in V1 is observed on average 156 ms after fixation point offset (Super et al. 2004). When indeed V1 presaccadic activity originates in the FEF, this would imply a conduction time of about 100 ms.

This estimate of time window relative to the appearance of a discriminated object in which the FEF is involved in attentional deployment is supported by a number of other studies. TMS of the FEF about 40 ms before presentation of a DT has been reported to be effective in changing perceptual performance (Grosbras and Paus 2003) in humans. In Neggers et al. (2007) a brief train of three consecutive pulses centered around 30 ms before DT presentation was also effective in disrupting the coupling between eye movements and visuospatial attention. Furthermore, the lateralized EEG potential preceding saccades as measured over the FEF in the study by Gutteling et al. (2009), discussed earlier, was elevated around the same time shortly before and during DT presentation.

Therefore in the present study a single pulse is applied at either 60, 30, or 0 ms before the brief presentation of a DT (0 ms defined as halfway to the 120-ms duration of the DT). If we observe stronger effects for early rather than late TMS, the possibility of disturbed visual processing within the FEF itself as an explanation for the effects of TMS on the coupling of visual attention to eye movements can be ruled out with more confidence. If the IPS conveys the modulatory signals from FEF to the visual cortex, TMS on the IPS should yield similar effects on visuospatial attention later during saccade preparation, compared with TMS on the FEF.

Finally, the study by Neggers et al. (2007) offering a brief train of three TMS pulses to the FEF seems at odds compared with single-pulse FEF stimulation studies (Grosbras and Paus 2003; O’Shea et al. 2004; Ruff et al. 2006; Silvanto et al. 2006), who all report an enhancement of visual processing after stimulation of the FEF (albeit during visual fixation) instead of a disruption. At present, the precise effects of TMS on neuronal processing are not well understood and subject to considerable debate in the field, in that TMS can either facilitate or disrupt neuronal activation. This seems to be dependent on stimulation frequency (Fitzgerald et al. 2006) and the baseline level of excitability of the underlying cortex (Silvanto et al. 2008). Low-frequency repetitive TMS (rTMS; between 1 and 5 Hz) has been shown to inhibit cortical tissue and decrease activation (Fitzgerald et al. 2006; Maeda et al. 2000). High-frequency rTMS, however, can facilitate neuronal processing in the stimulated tissue (Pascual-Leone et al. 1994). The short-lived effects of single-pulse stimulation (effect duration of ~10 ms according to Ilmoniemi et al. 1997) can be either facilitating (Moliadze et al. 2003; Tomasono et al. 2008) or inhibiting (overview in Moliadze et al. 2003; Pascual-Leone et al. 2000), depending on stimulation location and time of stimulation. For saccadic eye movements, either facilitating or inhibitory effects can be found when the FEF is stimulated at visual target onset or after target offset but before saccade execution, e.g., during saccade preparation (Nyffeler et al. 2004). Therefore in the present study we stimulated the FEF...
with a single pulse per trial rather than a brief train of pulses, as in Neggers et al. (2007), otherwise using the same behavioral paradigm. When indeed a single pulse on the FEF can enhance visual processing (at saccade location) as reported by others, whereas a brief train disrupts it as in Neggers 2007, one might relate the present findings with other single-pulse TMS studies on the FEF with more confidence.

METHODS

Participants

Ten right-handed participants (five male, five female) were selected for all experiments (three of the authors participated). All participants had normal or corrected-to-normal vision and were screened beforehand for metal implants and general MRI compliance (UMC Utrecht internal guidelines) and TMS compliance (Keel et al. 2001). The TMS stimulation protocol remained within the internationally accepted safety limits (Wassermann 1998). All participants were mentally healthy and all provided signed informed consent. The procedures were approved by the Medical Ethical Committee of the University Medical Center Utrecht (protocol nr. 05-020).

Before participating in the TMS experiment, participants engaged in a practice session. They were required to complete the behavioral paradigm without TMS to check whether they were able to make voluntary saccades toward a cued target while performing the discrimination task.

Experiment 1: fMRI

The subjects first participated in a short fMRI experiment, in which they performed an eye-movement task alternated with rest blocks, to activate the cortical oculomotor regions including the IPS and FEF involved in voluntary saccades.

APPARATUS. A 3-T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) was used to acquire the functional and anatomical images. The scanner was equipped with an eight-channel independent receiver SENSE coil, allowing parallel imaging (Neggers et al. 2008; Praussen et al. 1999). The stimuli were generated using the Presentation software (Neurobehavioral Systems) on a Plexiglas 1-m-wide screen. The screen was placed at about 2-m distance from the participant's head for metal implants and general MRI compliance (UMC Utrecht). The virtual image straight ahead of the participant at an effective computer monitor mounted 37 cm above the mirror. This resulted in a head-support 35 cm in front of a semisilvered mirror. The mirror participant's head was placed in a chin-rest with the forehead against a virtual image straight ahead of the participant at an effective computer monitor mounted 37 cm above the mirror. 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been determined as the minimal intensity of the TMS device at which the thumb showed visible twitches with the EyeLink II system (SR Research) on a Pentium PC on a 19-in. color monitor (screen size, 40 × 30 cm; refresh rate, 100 Hz; resolution, 1,024 × 768).

Eye tracking was realized by recording the position of the right eye with the EyeLink II system (SR Research) at 500 Hz using infrared (IR) video oculography. The video camera was mounted on a rigid head support and controlled by a Matlab script using the EyeLink Toolbox from the Psychophysic Toolbox (Cornelissen et al. 2002).

TMS pulses were administered by a Neopulse TMS device (Neotonus, Atlanta, GA) with an iron-core coil (Epstein and Davey 2002). The pulses were triggered by the PC running the stimulation paradigm in Matlab through a TTL pulse over the parallel port. The placement of the TMS coil was stereotactically guided with help of the individual fMRI activation maps registered with individual MRI anatomical images. A frameless stereotactic technique developed in-house was used, based on calibration of a subject’s craniotopic landmarks with the same landmarks in the individual MRI scan (for a detailed description see Neggers et al. 2004).

The activation t-maps obtained from the fMRI experiment (experiment 1) were superimposed on a three-dimensional (3D) rendering of the brain surface and skin for each individual in real time. The positions directly overlying the coordinates of maximum activation within FEF and IPS of both hemispheres as well as the vertex were pointed out with a 3D digitizer pen and marked on a tight-fitting cap placed on the participant’s head. The accuracy of this procedure is around 3 mm (Neggers et al. 2004), sufficient for TMS affecting about 1 to 2 cm of cortical tissue (Bohning et al. 2001). fMRI-guided TMS was necessary because the interindividual locations of FEF and IPS are highly variable (see Fig. 2C).

BEHAVIORAL PARADIGM AND PROCEDURE. Before starting the experiment, the TMS output intensity was determined for each participant. The motor threshold of each hemisphere was measured, which was determined as the minimal intensity of the TMS device at which the thumb showed visible twitches ≥5 out of 10 times after stimulating the cortical motor area for the thumb (Schutter and Van Honk 2006). The latter procedure realizes individual TMS intensity adjustment correcting for differences in transfer of the magnetic field to the cortex and electric conductivity within the brain. The TMS output intensity in the experiment was 120% of the derived motor threshold (MT) (120% MT) for the corresponding hemisphere, whereas the vertex was stimulated at the same intensity as that of the hemisphere with the highest MT.

The TMS coil was stereotactically guided to one of the five stimulation areas for a particular session. The order in which areas of interest were stimulated was randomized over participants.

The experiment consisted of five stimulation sessions: left and right FEF, left and right IPS, and vertex. Each trial in a session consisted of a cue for the saccade, then presentation of the DT during which one TMS pulse was given. This was followed by a saccade and the subject’s report of the nature of a DT. The TMS pulses were delivered 60, 30, or 0 ms before DT perception. Per session, 216 trials were used, resulting in 24 repetitions for each analyzed condition.

All stimuli were presented on a light gray background. Each trial was preceded by a drift correction, performed after 500 ms of stable fixation on a central black fixation cross (0.52 × 0.52°), which was repeated when not correctly executed. If the drift correction was successful, three colored ellipses of 0.82 × 1.64° appeared on each side of the fixation cross, 5° from the center and horizontally aligned with a spacing of 0.54°. The colors of the ellipses from the periphery toward the center were red, green, and blue. Five premasks were superimposed on the left and right ellipse arrays; the three middle ones overlapped the three ellipses. The premasks were black and resembled a digital “8” shape (1.05 × 1.05°) because they are common on digital alarm clocks. Spacing between premasks was 1.09°. After a 700-ms delay the fixation cross was replaced by the saccadic cue (SC), a colored arrow in the shape of a triangle (0.58 × 0.52°). The arrow pointed in the direction in which the saccade should be made (left or right); the color referred to which ellipse the saccade should be made (red, green, or blue, isoluminant). This cue was presented with a random delay between 500 and 1,000 ms to avoid predictability of SC onset. The “Go signal” indicating the saccade could be made was marked by disappearance of the cue. At 60 ms after the Go signal, the premask in the green ellipse at the side of the cued saccade direction was replaced by a symbol resembling an “E” or a reversed “3” (randomly assigned), referred to as the DT. Simultaneously, the other premasks were replaced by randomly assigned distracters resembling a digital “2” or “5.” The distracters and target were presented for 120 ms. See Fig. IA for an overview of the stimuli and Fig. 1B for the stimulation paradigm in time. The location of the DT was always the same (the green ellipse on the side to which the saccade should be made) and the participants were aware of this; 180 ms after the Go signal, the distracters and DT disappeared and only the colored ellipses remained visible.

The participant’s cortex was stimulated with a single TMS pulse for each trial, at either 60, 30, or 0 ms before “DT presentation” (e.g., at 60, 90, or 120 ms after the Go signal). “Time of DT presentation” is defined here as half the time that DT was present on screen (e.g., 60 ms after DT onset). Since DT was presented from 60 to 180 ms after the Go signal, DT “presentation time” equals 120 ms after the Go signal. In contrast to other studies using visual targets (most notably Schmolesky et al. 1998) the onset of the display of the target and distracters as used in the present study did not result in a net luminance change. Thus the current design avoids any exogenous capture of attention by the target onset and tests presaccadic facilitation of visual discrimination prior to the onset of an endogenous saccade. The presently used display method most likely results in a different and less-vigorous onset of neuronal activity in visual cortex neurons, compared with sudden onsets with significant overall luminance changes (see Schmolesky et al. 1998). Therefore we assume that with respect to the net activation in the visual cortex elicited by the DT stimulus, the “presentation time” is best approximated by the moment halfway between the 60- to 180-ms presentation time of the target. The latter is important for our a priori choice of TMS–DT intervals (see INTRODUCTION) based on neuronal transmission estimates.

Neggers and colleagues (2007) deployed a train of three pulses at 60, 30, and 0 ms before DT presentation, to increase the likelihood of obtaining a TMS effect, which was estimated to be optimal around 34 ms before DT presentation (see INTRODUCTION for the motivation). The present study aimed to determine which of those three pulses was responsible for the observed effects of performance disruption, thus deploying a single pulse on either of the three stimulation times (60, 30, or 0 ms before DT presentation). The stimulation times were pseudorandomized over the trials, resulting in an equal distribution of one third of the trials for each stimulation time.

The first task for the participants was to execute the saccade as cued. This meant they had to fixate their eyes in the middle of the screen and observe the arrow presented there until it disappeared—only then were the participants allowed to execute the saccade as prompted, in the cued direction and toward the cued colored ellipse. The second task for the participants was to report the identity of the DT (press the “F” key for an “E” or the “J” key for a reversed “3”). After reporting, the ellipses disappeared and the fixation cross reappeared, indicating the start of a new trial. The subjects were instructed to direct their saccades as correctly as possible to the instructed target, without attempting to look at any of the other objects.

The above-cited settings resulted in 36 possible conditions for a saccade trial per stimulation session of 216 trials: 2 cue sides (left or right), 3 locations (red, green, blue) × 2 DT identities (“E” or reversed “3”), and 3 TMS times (60, 30, or 0 ms before DT presentation). The identity of the DT was not expected to yield a difference in performance and thus the corresponding data were pooled. Moreover, the present study aimed at comparing data from trials with contralateral versus trials with ipsilateral saccades, meaning that data from trials with leftward saccades during right-
sided FEF stimulation could be pooled with data from rightward saccades during left-sided FEF stimulation for the contralateral condition. Pooling was performed vice versa for stimulation ipsilateral to saccade direction. Data from trials during vertex stimulation were neither contra- nor ipsilateral with respect to saccade direction and thus were also pooled. The resulting 9 conditions (3 locations × 3 TMS times) were presented for each of the five sessions (contra- and ipsilateral FEF, contra- and ipsilateral IPS, and vertex stimulation). For 216 trials per session there were effectively 24 repetitions per condition.

DATA ANALYSIS. To determine whether a proper saccade was made, the onset of a saccade was detected using a velocity threshold of 30°/s.

saccades that landed would have influenced discrimination performance. Furthermore, saccades during left-sided FEF stimulation for the contralateral condition. Pooling was performed vice versa for stimulation ipsilateral to saccade direction. Data from trials during vertex stimulation were neither contra- nor ipsilateral with respect to saccade direction and thus were also pooled. The resulting 9 conditions (3 locations × 3 TMS times) were presented for each of the five sessions (contra- and ipsilateral FEF, contra- and ipsilateral IPS, and vertex stimulation). For 216 trials per session there were effectively 24 repetitions per condition.

FIG. 1. A: schematic overview of the different frames constituting the visual stimulation paradigm for the transcranial magnetic stimulation (TMS) experiment (experiment 2). After successful drift correction, 6 colored ellipses (in A, indicated here by gray scales clarified by R, G, and B letters and an arrow, which are not visible on the computer screen) were shown containing 8-shaped masks. After 500 ms a central colored arrow appeared, indicating the target (saccade target [ST]) to which the saccade should be made. The arrow disappears after a randomized presentation interval of 500–1,000 ms (= Go signal). At 60 ms after the Go signal, the discrimination target (DT, consisting of an “E” or a mirrored “3”) appeared at the left or right green ellipse location; the other masks were replaced by 2- or 5-shaped distracters. After disappearance of DT, the trial ended and the participant had to report the target identity by pressing a button without time pressure. B: timescale of the events during a trial in the TMS experiment (experiment 2). Drift Cor. drift correction; saccadic cue: colored arrow indicating ST (see A). DT, “E” or mirrored “3”. The vertical arrow indicates the period at which the TMS pulse was delivered to the left or right frontal eye field (FEF), left or right intraparietal sulcus (IPS), or vertex, at 60, 30, or 0 ms before perceiving DT (determined as being halfway to DT presentation time). Times are expressed relative to the saccade Go signal (disappearance of the saccade cue).

For each participant the proportion of correct responses and the average saccade latency were calculated for the different experimental conditions. Saccade latency was defined as the time period between the Go signal (disappearance of the arrow cue) and saccade onset. The correct response ratios as well as the average individual saccade latencies were tested per stimulation sessions in repeated-measures ANOVAs for effects of saccade target position (TARGET), stimulation site (SITE: contra- or ipsilateral cortical stimulation with respect to saccade direction, or vertex), and the timing of TMS (TIME). Leftward and rightward saccades with the same target eccentricity (the same color ellipse as that of the cued target) were pooled because the previous study showed no significant difference between hemisphere stimulations (Neggers et al. 2007). The level of significance was set at P < 0.05.

RESULTS
Experiment 1: fMRI

Ten participants took part in an MRI experiment aimed at localizing the FEF and IPS for each subject individually. Here, participants made pro- and antisaccades in rapid succession in the scanner in a series of short blocks with fixation periods in between.

Saccade blocks versus fixation

Figure 2A shows a 3D cortical rendering with superimposed suprathreshold FEF and IPS activity during the saccade blocks, compared with the fixation blocks, for a single representative participant, in native space. This is a screenshot from the stereotactic software as used during fMRI-guided stereotaxy (Neggers et al. 2004). Figure 2B depicts an axial slice through the FEF and IPS, with activation t-maps overlaid, for one participant.

Figure 2C depicts an average MNI normalized brain with the coordinates of maximum activation within the left and right FEFs and IPS, for all 10 participants. Although the maxima cluster around the zones is known to entail human FEF and IPS (Koyama et al. 2004), there is considerable variability.
Experiment 2: TMS

In experiment 2 a TMS pulse was delivered over the individual left or right FEF, left or right IPS, and vertex, as localized using fMRI in experiment 1.

EXCLUDED TRIALS. Trials were excluded from analyses when saccades were made too early (to prevent foveal vision of DT) or landed too far away from the intended saccade target (see METHODS” for details). For one of the 10 participants <30% of trials remained for analysis only and thus this subject was excluded from analysis. For the remaining subjects, on average 51% of the trials entered analysis. The inclusion criteria for trials were strict because foveation of a DT due to saccades made too early would artificially improve discrimination performance. It is also important to ensure that indeed the instructed target was foveated to be able to validly attribute variation in target-discrimination performance to saccades to a certain target. Because our focus was on selective attention, it was of utmost importance that all saccades to noninstructed targets were excluded.

The number of trials excluded was independent of the area stimulated with TMS [ANOVA: F(4,1) = 2.035, P = 0.296]. For all the other experimental factors, only the factor TARGET resulted in a significant difference in the number of accepted trials [TARGET: F(2,18) = 4.66, P < 0.05]: slightly more trials were generally accepted for the central saccade target position (48 and 49% on average for inner or outer target positions, respectively, and 54% for the central target position).

DISCRIMINATION PERFORMANCE COMPARED FOR ALL TMS SITES. For the discrimination performance of all TMS sites and conditions, see Figs. 3 and 4 in the following text. First, we ran an omnibus ANOVA on all experimental factors to test whether effects of TMS on discrimination performance differed across the stimulated sites. The present experimental design did complicate a full-factorial ANOVA somewhat: the factor laterality (contra- or ipsilateral of TMS) cannot be included for vertex stimulation because the vertex is not hemisphere-bound, as opposed to the FEF and IPS. Therefore we ran an overall ANOVA with the factors SITE (IPS, FEF), LATERALITY (contra- and ipsilateral of stimulated hemisphere), TARGET, and TIME. This analysis ignores vertex stimulation data, but does allow a full-factorial ANOVA including laterality.

The quadratic contrast for the factor TARGET (modeling the reversed V-shape of the TARGET × performance graph) was significant [F(1,8) = 30.73, P < 0.001], indicating a clear coupling of saccade planning and spatial discrimination performance, consistent with previous findings (Deubel and Schneider 1996; Neggers et al. 2007). This contrast is used as the main indication for the influence of saccade target location on discrimination performance in the following analyses.

Here, the interaction SITE × TARGET × LATERALITY was significant [F(2,16) = 3.892; P < 0.05], implying that the specific and lateralized influence TMS has on the dependence of discrimination performance on saccade target is different for FEF compared with IPS stimulation.

The latter justifies further testing of IPS and FEF stimulation data separately to determine what the specific effects of TMS are for combinations of experimental factors. In the subsequent tests the effects are also tested against vertex stimulation.

FEF STIMULATION: DISCRIMINATION PERFORMANCE. The percentage of correctly identified DTs was considered as a function of saccade target position, TMS location, and TMS timing in a separate ANOVA for FEF data only. TMS location (factor SITE) now could be FEF contra- or ipsilateral to saccade direction, or vertex. Figure 3A depicts the discrimination performance, averaged over nine subjects, for TMS on the FEF ipsi- or contralateral to saccade direction and for vertex stimulation.
Influence of TMS site. The effect of the target location of the saccade in preparation on discrimination of the letter probes was largest for TMS on the FEF contralateral to saccade direction [see Fig. 3A; TARGET × SITE: F(1,8) = 5.8; P < 0.04, quadratic contrast for TARGET].

Because the effect for the factor SITE was significant, separate ANOVAs were run for the comparison of contra- with ipsilateral TMS and for the comparison between contralateral and vertex stimulation. For the comparison contralateral and ipsilateral TMS, the quadratic interaction TARGET × SITE was significant [F(1,8) = 5.67; P < 0.05]. For the comparison contralateral and vertex TMS, the quadratic interaction TARGET × SITE was significant at the trend level [F(1,8) = 4.095; P = 0.078].

Influence of TMS time. As can be seen in Fig. 3A, the influence of TMS on the coupling between discrimination performance and saccade target seems to decrease with TMS time. This effect seems most profound for FEF stimulation contralateral compared with ipsilateral of saccade direction. These effects were investigated statistically for the comparison contralateral versus ipsilateral (to saccade direction) stimulation of the FEF and contralateral FEF versus vertex stimulation and separately for the comparison inner-central and outer-central saccade target locations.

The TMS-induced difference (contralateral vs. ipsilateral FEF) between the performance increase for coinciding ST and DT (DT is always located at the center ellipse), compared with the inner ST location, is strong for the first TMS stimulation time, 60 ms before DT presentation, but decreases linearly with time until it is absent for 0 ms before DT presentation [TARGET × SITE × TIME: F(1,8) = 7.08; P < 0.05; linear contrast for the factor TIME; the quadratic contrast for TIME was not significant: F(1,8) = 0.004]. For the comparison of discrimination performance for the outer versus central target this effect was neither linearly [TARGET × SITE × TIME: F(1,8) = 0.31; linear contrast for the factor TIME] nor nonlinearly dependent on time [TARGET × SITE × TIME: F(1,8) = 0.38; quadratic contrast].

The comparison of TMS-induced performance changes for contralateral FEF versus vertex stimulation yielded no significant influences for TMS timing, for either the comparison inner-central or outer-central discrimination performance increases.

FEF STIMULATION: SACCade LATENCY. The latency of saccades was analyzed as a function of saccade target position, TMS location, and TMS timing. Figure 3B depicts the saccadic latencies, averaged over nine subjects, for TMS on the FEF ipsi- or contralateral to saccade direction.

Overall, the site of TMS (contra- or ipsilateral FEF stimulation, vertex) did not influence either the saccade latency [SITE: F(2,18) = 0.90] or the saccade target location [TARGET: F(2,18) = 0.21]. Saccade latency increased linearly with the time of TMS [linear contrast of TIME: F(2,18) = 16.21; P < 0.001; quadratic contrast n.s.: F(2,18) = 0.88]. Saccade latency changes over time depended, at the trend level, on the site of TMS [TIME × SITE: F(16,4) = 2.575; P = 0.056], indicating that effects of TMS on saccade latency compared with control stimulation differ for each timing condition. Therefore three separate analyses were performed for each TMS timing level.

For TMS stimulation at −60 ms (i.e., 60 ms before DT presentation), no effects of site or saccade target on saccade latency were observed [SITE: F(2,16) = 1.84; P = 0.19; TARGET: F(2,16) = 0.14].

For TMS stimulation at −30 ms, mainly latencies for saccades contralateral to the stimulated FEF decreased compared with TMS on the vertex [SITE: F(1,8) = 6.82; P < 0.05]. The other combinations of sites (ipsilateral vs. vertex, ipsilateral vs. contralateral) did not yield significant effects.

For TMS stimulation at 0 ms, no effects of site or saccade target on saccade latency were observed [SITE: F(2,16) = 0.39; TARGET: F(2,16) = 0.30], nor did any of the interactions test as significant.

IPS STIMULATION: DISCRimination PERFORMANCE. Figure 4A depicts the discrimination performance, averaged over nine subjects, for TMS on the IPS ipsi- or contralateral to saccade direction and for TMS on the vertex (control site).

Influence of TMS site. The effects of TMS on the performance increase for coinciding ST and DT seem to be qualitatively different for IPS stimulation, as observed for FEF stimulation (see Fig. 4A). This was confirmed by the overall full-factor ANOVA including both IPS and FEF stimulation data reported earlier. In general, the discrimination perfor-
mance seems to increase for all three saccade target locations for IPS stimulation compared with vertex stimulation (“elevated V-shape”), whereas the advantage of coinciding ST and DT compared with other saccade target locations is comparable (“similar V-shape sharpness”). Note that for FEF stimulation, TMS induced a “sharpening” of the reverse V-shape and not a general “elevation.” Separate ANOVAs were conducted for the comparison of contra- versus ipsilateral TMS and between contralateral and vertex stimulation (the control condition).

Indeed, for the comparison ipsilateral versus vertex TMS, the site of TMS had a significant influence on discrimination performance [SITE: F(1,8) = 7.24; P < 0.05]; the quadratic interaction TARGET × SITE was not significant [F(1,8) = 0.18]. No significant effects were found for the comparison contralateral versus ipsilateral TMS nor for contralateral versus vertex TMS.

**Dependence on TMS time.** In Fig. 4A, the reported influence of TMS on the general discrimination performance level (for ipsilateral IPS vs. vertex stimulation) seems to be strongest for TMS time at 30 ms before DT presentation. This is somewhat later compared with TMS effects for FEF stimulation. However, none of the comparisons between stimulation sites and times that were tested for the FEF reached significance.

IPS STIMULATION: SACCADE LATENCY. The latency of saccades was analyzed as a function of saccade target position, TMS location, and TMS timing. Figure 4B depicts the saccadic latencies, averaged over nine subjects, for TMS on the IPS ipsi- or contralateral to saccade direction. The same combinations of factors as those for FEF stimulation were statistically assessed to detect an influence of TMS timing or site on saccade latency.

The only significant effect that was observed was that the time of TMS did influence saccade latency, reflecting a linear increase of saccade latency with TMS time [linear contrast of TIME: F(2,18) = 77.24; P < 0.0001] similar to that for FEF stimulation. This increase was not dependent on the site of TMS [TIME × SITE: F(16,4) = 1.09; P = 0.38].

**DISCUSSION**

The present study demonstrates that the FEF plays a key role in shifting focus of visual attention toward the target of a saccade, shortly before it is executed. The FEF and IPS were first individually localized with fMRI. It was observed that fMRI-guided TMS on the FEF contralateral to saccade direction 60 ms before the presentation of a DT can increase the discrimination performance of a target presented at the goal location of the upcoming saccade, thus strengthening the coupling between saccadic eye movement preparation and visuospatial attention. This effect was smaller at 30 ms and absent at 0 ms before DT presentation. Furthermore, saccade latency decreases were observed for TMS on the FEF 30 ms before DT presentation, again for saccades contralateral to the stimulated FEF. It is unlikely that the TMS-induced saccade latency decreases resulted in the enhanced discrimination performance for TMS on the contralateral FEF; the rigorous analysis ensured that trials were saccades arrived at the DT before DT offset were excluded from analyses and thus foveation of the DT in trials with shorter latencies can be ruled out. Furthermore, TMS on the FEF resulted in reduced latencies only 30 ms before DT presentation, whereas discrimination performance effects are maximal for TMS at 60 ms before DT presentation and decrease linearly with TMS timing.

The effects of IPS stimulation on discrimination performance differed substantially from effects of FEF stimulation. TMS on the IPS resulted in general ipsilateral increases in discrimination performance at all locations, irrespective of the target of the saccade, whereas TMS on the FEF led to enhanced performance only for targets at the upcoming saccade goal. Unlike for the FEF, effects of TMS on IPS were not dependent on TMS timing.

TMS stimulation on the FEF, IPS, and vertex induced an increase in saccade latency with an increasing Go signal TMS interval. This effect is therefore most likely due to a general effect of TMS, for example, a warning effect increasing alertness induced by the audible or sensible nonneuronal effects of TMS.

**Enhancement versus suppression of performance as a result of TMS**

Interestingly, a preceding study (Neggers et al. 2007), using a short train of three TMS pulses (at 110% MT) at 60, 30, and 0 ms before DT presentation in an otherwise identical stimulus paradigm, resulted in a decrease of discrimination performance gain for coinciding saccade and DTs, contralateral with respect to vertex TMS. The reported influence of TMS on the general discrimination performance level (for ipsilateral IPS vs. vertex stimulation) seems to be strongest for TMS time at 30 ms before DT presentation. This is somewhat later compared with TMS effects for FEF stimulation. However, none of the comparisons between stimulation sites and times that were tested for the FEF reached significance.
to the stimulated FEF. The present study, however, applying only a single pulse at 120% MT at the contralateral FEF, reports an increase of discrimination performance. As stated in the introduction, effects of TMS on neuronal processing are reported to be highly variable. The inhibiting or enhancing effect of TMS is highly dependent on timing, location, duration, and—importantly—frequency or even an interaction of frequency and duration as shown by Aydin-Abidin et al. (2006). In a direct comparison study of single-pulse and repetitive stimulation, single-pulse TMS did not show any significant effect on motor-evoked potential size. This was in contrast to the observed decreased cortical excitability after 5 or 15 pulses (Huang and Rothwell 2004) or as many as 1,600 pulses (Pascual-Leone et al. 1998). When regarding the three pulses applied in rapid succession in our preceding study (Neggers et al. 2007) as a high-frequency—short-duration stimulation protocol, effects different from a single pulse of TMS as used in the present study could be expected (Fitzgerald et al. 2006). Even though it is debatable whether a train of 3 pulses is comparable to longer high-frequency stimulation, it is clear from all preceding comparative studies that successive pulses can yield different or even opposite effects compared with single pulses.

For single-pulse TMS the moment of stimulation in visual paradigms is of utmost importance. Whereas a single pulse during saccade execution can disrupt saccade performance, it has been repeatedly shown that single-pulse TMS applied before presenting a visual cue has facilitating effects, resulting in reduced reaction times in studies by Grosbras and Paus (2002, 2003) and increased fMRI activity in the peripheral visual field in the occipital cortex (Ruff et al. 2006). It has been suggested that TMS actually adds noise to an intricate process of neuronal signaling reducing the processing efficacy, although that view has been challenged (Harris et al. 2008). Only a few studies investigated interactions of a magnetic pulse with electrical neuronal signaling directly (Moliadze et al. 2003). Much more research on physiological mechanisms underlying TMS effects is required to understand the effects of different TMS intensities and frequencies. Still, in the light of the studies discussed earlier, it can be argued that one realizes an enhancement of “normal” neuronal signaling when the current added by TMS somewhat resembles the natural neuronal process in the neuronal tissue under investigation. A disruption of function can be expected, however, when the TMS-induced current is remote from the operations the neuronal tissue under investigation normally performs. This might explain the reversal of the TMS effect in the present study compared with the preceding study (Neggers et al. 2007). That is, a brief but vigorous pulse of activity is normally observed in the primate FEF around saccadic eye movements (Bruce and Goldberg 1985), probably to some extent resembling the pattern a single TMS pulse evokes in the FEF (for evidence of similarity between TMS and internally evoked BOLD responses in the motor cortex, see Bohning et al. 1999). Therefore a single pulse could lead to facilitation of FEF functioning. A brief train of bursts, however, is not normally observed around a single saccade in the FEF, which therefore would suppress normal FEF functioning. Importantly, we do not imply that effects of a single TMS pulse resemble real neuronal saccade control processes in every way (otherwise TMS should be able to trigger overt saccades), but rather that the induced current resembles normal neural activation, albeit evoked in a larger, less-specified area.

Timing of the TMS effects: implications for pathways

It has been suggested that the influence of the FEF on early visual processing is realized by corticocortical connections between the FEF and early visual cortex (Moore et al. 2003; Neggers et al. 2007; Ruff et al. 2006; Super et al. 2004). That is, electrical stimulation of FEF neurons induces activation in V4 (Moore et al. 2003) for matching movement and receptive fields. V1 neurons show a clear modulation before a saccade is initiated (Super et al. 2004) and TMS on the FEF during fMRI results in activation of V1 (Ruff et al. 2006). All the latter studies were performed during fixation. Recently, it was demonstrated that this feedback connection from the FEF to the visual cortex might subserve the well-known modulation of visual processing during saccade preparation, by disrupting this coupling with a short train of TMS to the FEF (Neggers et al. 2007). Importantly, TMS was administered before any information regarding the to-be discriminated target could have reached the FEF, indicating that the actual influence of the FEF over visual processing is exerted elsewhere, most likely the visual cortex. However, the direct neurophysiological effect of TMS might outlast the 3 ms we assumed as the time TMS affects neuronal processing (Ilmoniemi et al. 1997). In fact, longer-lasting neuronal TMS effects were recently reported (Allen et al. 2007; Paus et al. 2001). This residual TMS signal could then disturb incoming information within the FEF, allowing the conclusion that attentional processing is implemented in the FEF itself rather than through recurrent connections to the visual cortex. The present results, however, contradict the latter: effects of TMS were strongest 60 ms before DT presentation and gradually disappeared for later time intervals. When neuronal effects induced by TMS stay present within the FEF for some time, the enhanced discrimination performance should have remained or increased for later TMS administration. Therefore the present study can conclude with more certainty that effects of FEF stimulation on the coupling of visuospatial attention to eye movement preparation are induced by the influence the FEF has over another region, most likely the visual cortex. Finally, we provided further support for this notion in a recent EEG study by Gutteling et al. (2009), using the exact same behavioral paradigm as that in the present study. It was reported that presaccadic FEF activation lateralized to saccade direction preceded occipital activation lateralized in the same manner and peaked around the same time TMS on the FEF was most effective in the present study.

It should further be noted that FEF signals can reach the visual cortex not only directly (Schall et al. 1995b), but also through known projections to the superior colliculus in the midbrain (Sommer and Wurtz 2000), from which these signals can be relayed to extrastriate areas.

Involvement of IPS

Previous reports argued that effects of FEF stimulation on the visual cortex are relayed through the IPS because effects were found only when a discrimination stimulus was presented and direct connections should have induced effects irrespective of visual stimulation (Moore et al. 2003; Ruff et al. 2006). In
line with this, electrical stimulation of monkey FEF was found to modulate activity as measured by fMRI in early visual areas, but the effect was highly dependent on whether a visual stimulus was present (Ekstrom et al. 2008). However, in the present study, in contrast to TMS on the FEF, effects of IPS stimulation on visual discrimination performance were present for all conditions, irrespective of the target of the upcoming saccade. Furthermore, effects of IPS stimulation did not clearly depend on TMS timing. Finally, the only significant effect of IPS stimulation was observed for IPS stimulation ipsilateral to saccade direction, whereas contralateral effects were found for FEF stimulation. When the FEF indeed enforces a coupling of visuospatial attention to the saccade goal by means of projections to the visual cortex, TMS effects were expected mainly for saccades contralateral to the stimulated FEF. That is, the visual cortex codes contralateral retinotopic space, the FEF contralateral saccades (Bruce et al. 1985), and the FEF projects to ipsilateral visual cortex (Moore and Armstrong 2003). As we observed clear differences in dependence of TMS effects on the local (e.g., the red, green, or blue) eye-movement target (clear dependence for FEF; no dependence for IPS) and in laterality of the effects one can argue that direct connections from the FEF to the visual cortex cause the reported influences, or some other pathway, but not a pathway including the IPS.

Interestingly, in a recent study (Ruff et al. 2008) concurrent fMRI/TMS revealed that FEF stimulation induced activation in the visual cortex, greatly depending on the coded visual eccentricity; TMS-evoked BOLD responses were large and positive for areas representing the visual periphery and negative for areas representing foveal vision. This supports the notion that the influence of the FEF over the visual cortex subserves saccade preparation: saccades are usually made into the periphery. IPS stimulation in the study by Ruff and colleagues (2008), however, resulted in markedly different global effects—irrespective of the eccentricity coded in the specific zones of affected visual cortex. The latter is in agreement with the present report, observing a saccade-related enhancement of visual attention after FEF stimulation and a general improvement of visual performance for IPS stimulation. Finally, our recent EEG study by Gutteling et al. (2009) mentioned earlier, using the exact same behavioral paradigm, did not detect any presaccadic IPS activation lateralized to saccade direction that was larger than a control (e.g., fixation) condition, as was found for the FEF and the occipital lobe.

Effects of TMS on saccade latencies

First, saccade latency increased slightly with later TMS times. Because this effect was the same for all TMS sites, including the vertex, it is most likely caused by a general, nonneuronal warning effect of the (audible and sensible) TMS pulse. Second, saccade latencies were site-specifically but moderately shortened by TMS (only for FEF stimulation at t = −30 ms) in the present study, in contrast to the absence of any latency effect in Neggers et al. (2007) using a similar paradigm with a brief train of TMS pulses at the same interval. The results, however, can be reconciled with other studies that did observe TMS effects on saccade latency (mainly increases) in specific and narrow time windows only. TMS on the FEF 60 ms before saccade initiation delays prosaccades (Priori et al. 1993). Antisaccades were delayed when stimulating the FEF 100 ms after target presentation (~165 ms before saccade onset), but not at 80 or 120 ms (Terao et al. 1998), and prosaccades for TMS at that time interval were unaffected. In the present study TMS was delivered much earlier before saccade onset than 60 ms, known to delay prosaccades (Priori et al. 1993). Possibly, the narrow time window in which TMS is effective in delaying saccades reflects buildup of a signal directly driving saccades rather than the earlier saccade preparation/anticipation-related signals known to exist in the FEF (Everling and Munoz 2000) that we might have tampered with, not necessarily leading to direct motor effects. This could explain the minimal effect on saccade latency in the present study, in the other direction than reported for TMS on the FEF later during the target–saccade interval (Priori et al. 1993).

Conclusions

The present study demonstrates that the FEFs are responsible for directing our visuospatial attention to the target of a saccade in preparation. TMS could enhance the coupling of spatial attention to the target of the saccade in preparation when administered to the FEF well before visual information regarding the discriminated probe could have reached the FEF—and this effect gradually disappeared for later stimulation times. This indicates that the FEF is probably the driving source of visuospatial attention shifts, although it cannot be the site at which visual information from the outer world is actually selectively filtered. Based on the present findings and other recent reports from single-cell neurophysiology, EEG, fMRI, and TMS mentioned earlier, we propose that the FEF directs selective visuospatial attention by influencing the visual cortex directly through recently discovered anatomical connections (Moore et al. 2003; Super et al. 2004). The effects of TMS on the IPS were a global improvement of visual performance, irrespective of the saccade target. Therefore the pathway from the FEF by which the visual cortex is influenced shortly before a saccade most likely does not involve the IPS.

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