Transcranial Magnetic Stimulation of the Human Frontal Eye Field: Effects on Visual Perception and Attention

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Abstract

■ When looking at one object, human subjects can shift their attention to another object in their visual field without moving the eyes. Such shifts of attention activate the same brain regions as those involved in the execution of eye movements. Here we investigate the role of one of the main cortical oculomotor area, namely, the frontal eye field (FEF), in shifts of attention. We used transcranial magnetic stimulation (TMS), a technique known to disrupt transiently eye-movements preparation. We hypothesized that if the FEF is a necessary element in the network involved in shifting attention without moving the eyes, then TMS should also disrupt visuospatial attention.

For each volunteer, we positioned the TMS coil over the probabilistic anatomical location of the FEF, and we verified that single pulses delayed eye movements. We then applied TMS during a visuospatial attention task. In this task, a central arrow directed shifts of attention and the subject responded by a keypress to a subsequent visual peripheral target without moving the eyes from the central fixation point. In a few trials, the cue was invalid or uninformative, yielding slower responses than when the cue was valid. We delivered single pulses either 53 msec before or 70 msec after target onset.

Contrary to our prediction, the main effect of the stimulation was a decrease in reaction time when it was applied 53 msec before target onset. TMS over the left hemisphere facilitated responses to targets in the right hemifield only and for all cueing conditions, whereas TMS over the right hemisphere had a bilateral effect for valid and neutral but not invalid cueing. Thus, TMS interfered with shift of attention only in the case of right hemisphere stimulation: it increased the cost of invalid cueing.

Our results suggest that TMS over the FEF facilitates visual detection, and thereby reduces reaction time. This finding provides new insights into the role of the human FEF in processing visual information. The functional asymmetry observed for both facilitation of visual detection and interference with shifts of attention provides further evidence for the dominance of the right hemisphere for those processes. Our results also underline that the disruptive or facilitative effect of TMS over a given region depends upon the behavioral context. ■

INTRODUCTION

Attention can be oriented to different locations in the visual field in the absence of eye movements. These covert shifts of attention share a common neural basis with the planning of eye movements, that is, overt shifts of attention (Corbetta et al., 1998; Nobre et al., 1997; Kustov & Robinson., 1996; Schneider & Deubel, 1995; Johnson, 1994; Sheperd, Findlay, & Hockey, 1986). In this study, we focused on one important part of the common circuit, namely, the frontal eye field (FEF).

The FEF has been defined in nonhuman primates as an area in the frontal cortex from which low-threshold electrical stimulation (<50 μA) elicits contraversive eye movements, and where oculomotor activity can be recorded in single units (Bruce, Goldberg, Bushnell, & Stanton, 1985; reviewed in Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000). Three main categories of neurons have been identified: visual, motor, and visuomotor, discharging respectively at the onset of a visual target, when the saccade is executed, or both (Schall, 1997; Goldberg & Segraves, 1990). Thus, the FEF in monkeys can be viewed as an interface between visual processing and motor production, dedicated to the orienting system.

In humans, electrical stimulation in the vicinity of the precentral gyrus can elicit eye movements, suggesting the existence of a homologue of the monkey FEF (e.g., Godoy, Lüders, Dinner, Morris, & Wyllie, 1990; Rasmussen & Penfield, 1948). Brain imaging studies have reported that the hemodynamic correlates of neuronal activity significantly increased in the putative FEF during reflexive and voluntary eye movements. Although the location of the FEF is less accurately determined in humans than in monkeys, a significant number of those studies show that the human FEF lies near the junction between the precentral and superior frontal sulci (Lobel et al., 2001; Luna et al., 1998; Petit et al., 1993; reviewed in Paus, 1996). In addition, tasks requiring shifts of attention without eye movements as well as tasks

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requiring focused attention activate the frontal cortex in the region of the FEF (Hopfinger, Buonocore, & Mangun, 2000; Gitelman et al., 1999; Law, Svarer, Holm, & Paulson, 1997; Nobre et al., 1997; Corbetta, Miezin, Shulman, & Petersen, 1993). This indicates a functional overlap for visuospatial attention and eye movements (Corbetta et al., 1998; Sheliga, Riggio, & Rizzolatti, 1994). Brain imaging studies, however, simply establish an association between changes in the activity of a given neural structure and the performance of a task; a neural structure identified in such a way may not actually be ''necessary'' for the task. Thus, the question still remains unanswered whether the FEF is critically involved in visuospatial orienting even in the absence of eye movements.

Transcranial magnetic stimulation (TMS) allows us to address this issue. By delivering a brief and focal magnetic pulse over the scalp, we can induce a transient electrical current in the underlying brain tissue and thus modulate, during a very brief period of time, the activity of the targeted neuronal populations. We can thus infer causal links between that targeted region and the studied function. TMS is best known in cognitive neuroscience as a tool used to interfere with a given function by producing a ''virtual lesion'' (Pascual-Leone, Bartres-Faz, & Keenan, 1999; Ashbridge, Walsh, & Cowey, 1997). For instance, a train of stimulation (repetitive TMS, rTMS) over the supplementary motor area impaired performance of a complex sequence of finger movements (Gerloff, Corwell, Chen, Hallet, & Cohen, 1997); rTMS over occipital cortex induced scotoma (e.g., Amassian et al., 1998); speech was disrupted by rTMS over the inferior frontal cortex (Pascual-Leone, Gates, & Dhuna, 1991). Single-pulse TMS can also have a disruptive effect when applied at the appropriate time (e.g., for visual perception, Amassian et al., 1998; or manual reaction time [RT], Kammer & Nusseck, 1998). On the other hand, focal TMS can also be used to excite neural pathways: TMS over the primary visual cortex induces phosphenes and TMS over the primary motor cortex evokes motor potentials.

When applied over the FEF, TMS does not elicit eye movements (Müri, Hess, & Meienberg, 1991; Wessel & Kompf, 1991). Many authors, however, reported an interference with preparation and execution of saccades (Li, Olson, Anand, & Hoston, 1997; Thickbroom, Stell, & Mastaglia, 1996; Zangemeister, Canavan, & Hoemberg, 1995; Priori, Bertolasi, Rothwell, Day, & Marsden, 1993; Müri et al., 1991). The main reported effect of TMS applied over the FEF during saccadic preparation is an increase in latencies of voluntary saccades.

In the present study, we used single-pulse TMS to investigate further the role of the FEF in covert visuospatial attention. We reasoned that if the FEF is necessary to direct covert attention, then TMS applied over the FEF during a visuospatial attention task should affect performance for targets in the contralateral visual field. We applied TMS over the probabilistic location of the FEF targeted in each subject using a magnetic resonance image of the subject's brain and frameless stereotaxy. To verify that we were actually stimulating the FEF, we first applied single-pulse TMS during the performance of an oculomotor task. Based on previous studies (e.g., Thickbroom, Stell, & Mastaglia, 1996; Priori et al., 1993), we selected for further assessment of FEF function only subjects with statistically significant increase in the latency of saccades generated towards the contralateral hemifield. Then, we assessed the effect of single-pulse TMS on a visuospatial attention task performed without eye movements. In this task, a central cue directed the subject's attention to either the left or right hemifield (see Figure 1). Then a peripheral target appeared and the subject's task was to discriminate between short and long targets, responding as fast as possible by a keypress. Manual RTs are typically faster when subjects are able to anticipate target location (valid cue condition), as compared with neutral or invalid cues (Posner, Walker, Fridrcih, & Rafal, 1984). We expected that TMS applied over the FEF during the cue–target interval would disrupt advanced allocation of attention to the contralateral visual field, and thereby increase RT for valid cues. Following the same logic, TMS should decrease ipsilateral response times in the case of invalid contralateral cueing. As a control, we also stimulated a region in the temporal cortex during the same visuospatial attention task in another group of subjects. For each stimulation site, TMS and non-TMS trials were intermixed.

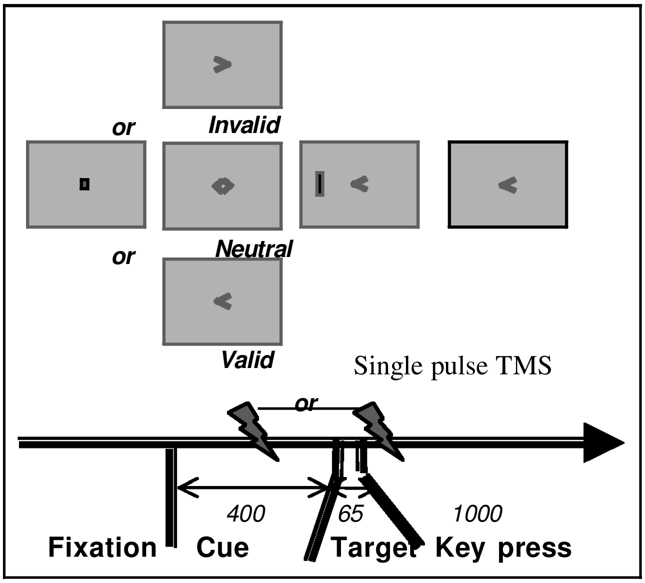


Figure 1. Visuospatial attention task: paradigm. The instruction was to maintain central fixation, shift attention in the direction of the cue (except for neutral cue), and respond to the appearance of the target by a keypress. Single-pulse TMS was delivered either 53 msec before the target or 67 msec after the target in about one trial out of three.

RESULTS

Auditory-Cued Saccades

This task served as a "functional marker" for the FEF: TMS applied shortly before the expected onset of a saccade has been shown to increase latencies, especially for contraversive voluntary saccades (Thickbroom et al., 1996). Data from 10 subjects were collected for the left and right FEF, each stimulated during auditory-cued saccades. Prior to the TMS part of the study, we determined the average latency of leftwards (190 msec ± 29 *SD*) and rightwards (175 ± 29 *SD*) saccades in each subject; single-pulse TMS was applied 50 msec before the subject's predicted saccade onset.

The analysis of group data showed a significant increase in latencies after TMS (as compared with trials without TMS) for both directions of saccades. After stimulation over the left FEF, the median latency increased on average by +6.2% (5.9% *SD*, paired t test, $p < .02$) and by 9.7% (7.2% *SD*; paired t test, $p < .004$) for leftwards (contralateral) and rightwards (ipsilateral) saccades, respectively. After stimulation over the right FEF, the average latency increased on average by +16.3% (12.4 *SD*; paired t test, $p < .0004$) for leftwards (contralateral) saccades and +12.1% (8.2 *SD*; paired t test, $p < .005$) for rightwards (ipsilateral) saccades.

We used individual statistics in order to select subjects for the subsequent visuospatial attention study. When tested individually, left FEF stimulation increased latency significantly in two subjects for leftwards saccades only, in three subjects for rightwards saccades only, and in three subjects for both directions of saccades (Wilcoxon, $p < .05$). Right FEF stimulation increased latency significantly in three subjects for leftwards saccades only, in one subject for rightwards saccades only, and in three subjects for both directions. Furthermore, previous TMS and intracranial stimulation studies, indicating that the human FEF controls mainly contralateral eye movements, as it is the case in monkeys (e.g., Ro, Cheifet, Ingle, Shoup, & Rafal, 1999; Müri et al., 1991; Godoy et al., 1990). We expected therefore that TMS over the FEF would have greater effect for contraversive saccades. We took this as an indication of FEF stimulation compared to nonspecific effect TMS could have. We restricted our criterion and selected only subjects in whom stimulation induced a higher increase for contraversive saccades. Five subjects showed this pattern (see Figure 2) for stimulation over the left FEF and five subjects for stimulation over the right FEF. Among those, two were included in both groups. Relative intensity of TMS, expressed as motor threshold, and saccadic latencies did not differ between the left and right FEF groups (Student's t test, $p > .9$).

Visuospatial Attention Task

Saccades and Error Rate

Off-line analyses of eye movement recordings were used to exclude trials in which a saccade or a blink had occurred. The number of such trials varied from 0 to 11.7% of the total number of trials. It did not differ between trials with and without TMS. There was no difference between the three groups of subjects (left FEF stimulation; right FEF and middle temporal cortex). Error rate ranged from 0.2% to 19% (mean 4.84; *SD* 4.14), without difference between groups of subjects. Error rate did not differ between trials with and without TMS. It is important to note, however, that the number of errors is too low to draw any definitive conclusions.

RTs without TMS (Figure 3)

After exclusion of trials with saccades, blinks, or errors, we calculated median RTs for each condition (Figure 3).

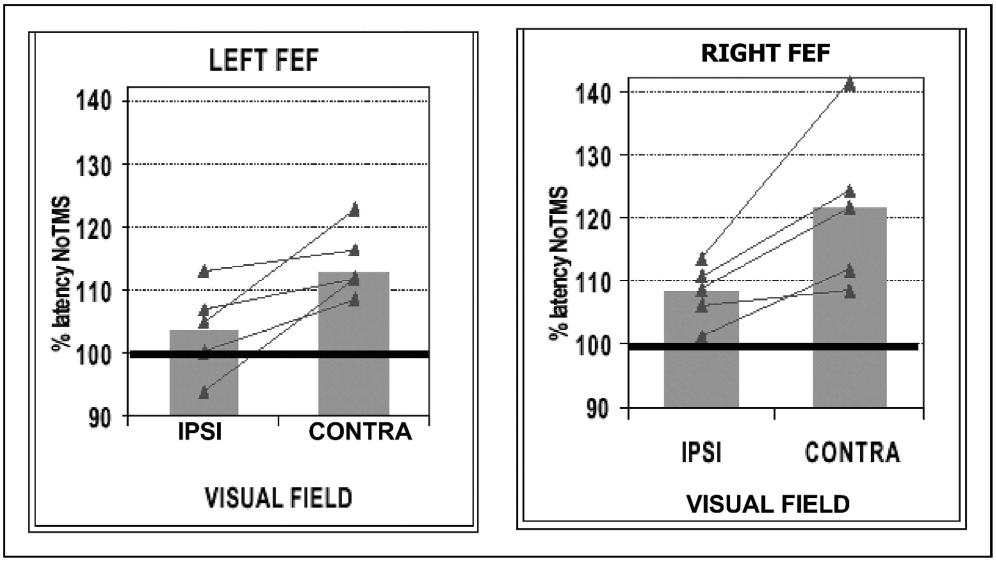
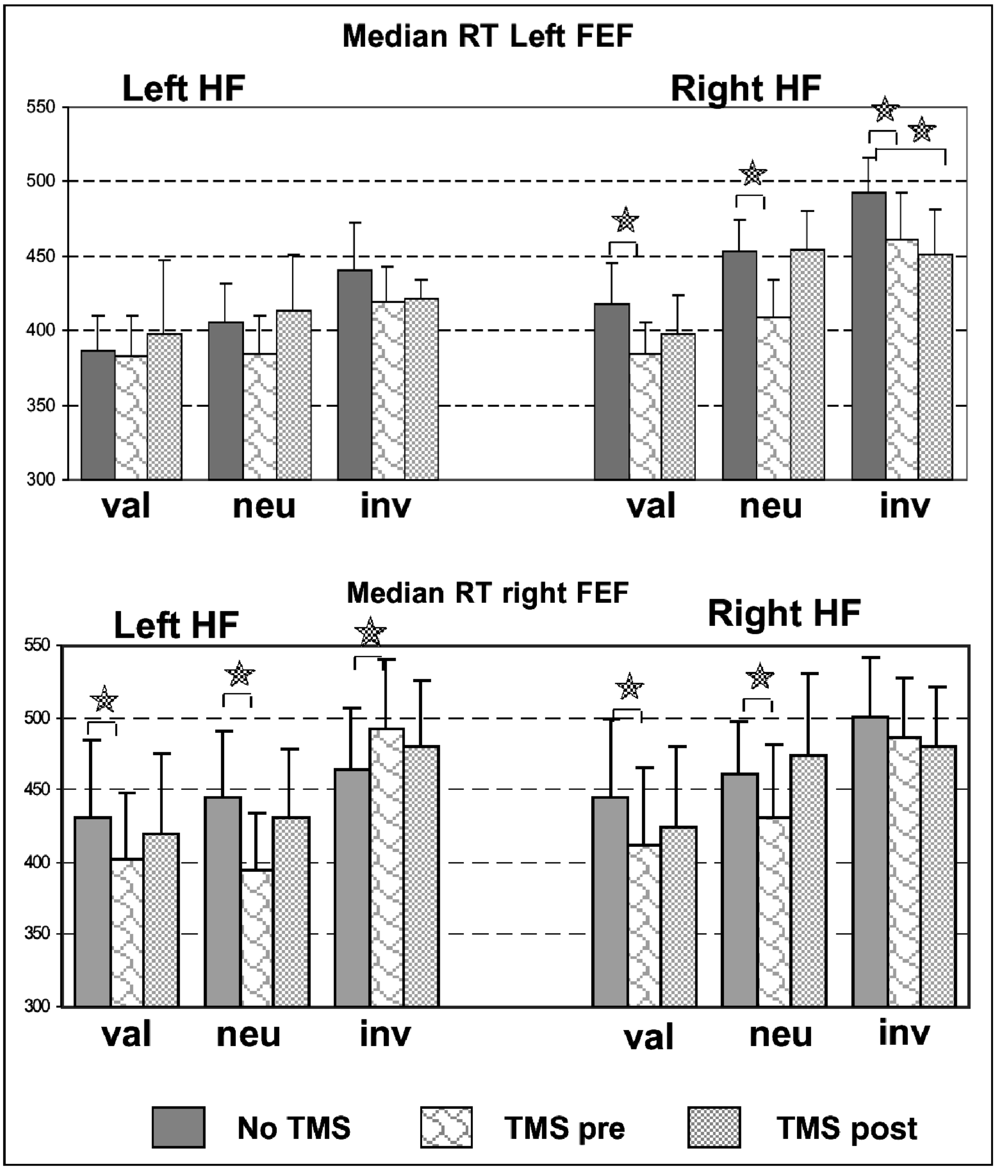


Figure 2. Oculomotor task. Results for the five subjects included in the left FEF group and for the five subjects included in the right FEF group. The saccadic latencies in trials with TMS are expressed as a percentage of the median latency in trials without TMS. The left part of each graph shows the latencies for saccades directed towards the hemifield ipsilateral to the site of stimulation; the right part shows latencies for saccades directed towards the contralateral hemifield. Lines represent individual data and vertical bars the average across five subjects.

Figure 3. Visuospatial attention task: Results. Median RT ($\pm SEM$) for trials without TMS, with TMS applied over the FEF 53 msec before the target and TMS applied over the FEF 67 msec after the target, averaged in each group of subjects. Stars indicate significant ($p < .05$) difference. HF = hemifield; val = valid cues; neu = neutral cues; inv = invalid cues.

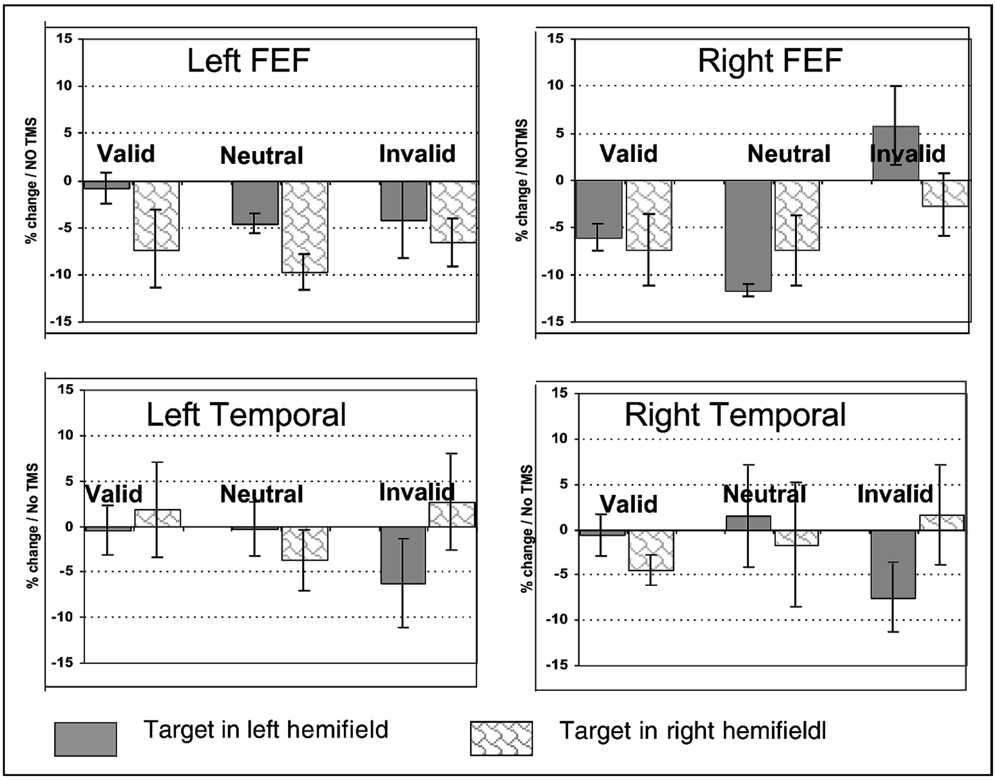


We first analyzed trials without TMS separately with group (i.e., left FEF, right FEF, and control) as between-subjects variable. This analysis (repeated-measure ANOVA, 16 subjects, three cueing conditions, two visual fields) showed a highly significant main effect of cue [$F(2,26) = 20.65$, $p < 10^{-4}$]. As expected, valid cues induced significantly faster RT than neutral or invalid cues. The averaged median RT was 430 msec in valid, 451 msec in neutral, and 487 msec in invalid condition. It did not differ between the three groups of subjects [$F(2,18) = .086$, $p = .967$]. To quantify the advantage of advance cueing, the benefit score was calculated as the difference between neutral and valid conditions expressed as a percentage of neutral RT. The disadvantage of invalid cueing was expressed by the cost score calculated as the percentage difference between invalid and neutral conditions. Benefit (median [SD]) left VF 4.46% (5.00); right VF 8.1% (6.47); cost left VF 11.17% (10.21), right VF 6.35% (9.45).

TMS over the FEF: Main Effect on Manual RTs (Figures 3 and 4, Top)

We performed an analysis of variance on the two groups of subjects having received TMS over the left or right FEF (five subjects in each group). The main effect of TMS over the FEF was a decrease in RT, highly significant across all cueing conditions [$F(2,16) = 20.25$, $p < 10^{-4}$]. This effect depended on the timing, being significant ($p < 4 \times 10^{-4}$) only when TMS was applied 53 msec before the target's onset (early TMS). When the pulse was delivered after the target's onset, we observed a tendency to decreased RT, which did not reach significance ($p = .14$). Contrasting the no-TMS condition with the early-TMS condition showed a three-way

Figure 4. Effect of TMS. Median RTs in trials with TMS before target are expressed as percent change of median RTs without TMS, namely, $(RT_{TMS}-RT_{NoTMS})/RT_{NoTMS}$. Within each group, average percent change across subjects (±*SEM*) is shown in each cueing condition for responses to targets in the right (light bars) or left (dark bars) visual field.



interaction between hemisphere stimulated, visual field, and the presence or absence of TMS [$F(1,8) = 6.36$, $p < .036$]. This interaction was explained by a difference in changes induced by TMS over the left and the right FEF, respectively. The post hoc comparisons showed that the stimulation of the left FEF during the cue–target interval decreased RTs significantly with ($p < .05$ corrected, Newmann–Keuls procedure), but only when the targets were presented in the contralateral (right) visual field. RTs were reduced by TMS in all three cueing conditions. Except for one subject who did not show the effect in the valid condition, we observed RTs reduction for all subjects, ranging from 25 to 57 msec (5.5–16.5%). In contrast, for the right FEF stimulation, TMS decreased RT for both ipsi- and contralateral targets. This was observed in all five subjects for valid and neutral cues. This decrease did not differ significantly between visual fields despite a tendency for a larger contralateral effect [$F(1,8) = 1.035$; $p > .33$]. For invalid cues, we observed an increase in RT in trials with TMS, for contralateral targets (+27 msec = +5.8%) and no effect for ipsilateral targets. No difference reached statistical significance in post hoc tests ($p > .28$).

To assess further these results, we conducted an ANOVA on the percent changes in RT induced by TMS in each condition [i.e., 100 × (TMS−NoTMS)/NoTMS]. For TMS applied before the target, the percent change showed a main effect of the target's hemifield [$F(1,8) = 10.77$, $p < .011$], reflecting that RT decreased more for contralateral targets. When tested in the left FEF group, TMS effect showed a significant difference between the left (−3.7%) and right (−8.1%) visual fields [$F(1,8) = 7.31$, $p < .027$]. In contrast, TMS effect did not differ between visual fields in the right FEF group [$F(1,8) = .22$, $p > .65$]. In this group, we observed a main effect of cue, reflecting that TMS decreased RT in valid and neutral but not invalid trials.

Effect of FEF TMS on Benefit and Cost

We observed a tendency to reduce RT more in neutral than in valid trials, resulting in a decrease in benefit. This difference was not statistically significant (specified contrasts tested separately for left and right FEF stimulation, $p > .5$), however. Direct analysis of the benefit score also showed that the decrease induced by TMS was not statistically significant [left FEF stimulation: $F(1,8) = .48$, $p > .5$; right FEF stimulation: $F(1,8) = .008$, $p > .9$], and was not consistent across subjects.

Analysis of the cost score showed a main effect of TMS [$F(1,8) = 10.11$, $p < .013$], a two-way interaction between TMS and hemisphere stimulated [$F(1,8) = 7.21$, $p < .027$], and a three-way interaction TMS × Hemisphere × Visual field [$F(1,8) = 6.03$, $p < .039$]. These statistics reflected an increase in the cost score of +19.8% for contralateral (left) targets and of +5.9% for ipsilateral targets after right FEF stimulation.

TMS over Temporal Lobe (Figure 4, Bottom)

As a control, we applied single-pulse TMS in the same visuospatial attention task over the left and right middle temporal cortex (Figure 4). The control group did not differ from the left and right FEF groups regarding the motor threshold, age, and sex. We did not observe significant changes in RT nor in error rates after TMS over the left or right temporal cortex [$F(1,18) = 0.73$, $p > .4$].

DISCUSSION

We hypothesized that if the FEF is necessary for visual orienting without eye movements, then TMS should impair performance in a visuospatial attention task. We observed decreased performance only when stimulating the right hemisphere and only when the cue was invalid, that is, when attention had to be disengaged and moved to the opposite hemifield. Interestingly, in the other conditions, we did not observe the predicted disruption but instead, we observed a facilitation due to TMS: when applied during the cue–target interval, single-pulse TMS decreased keypress response times to peripheral targets. While the left FEF stimulation decreased response times to contralateral targets only and for all cueing conditions, the right FEF stimulation had a bilateral effect observed for valid and neutral, but not invalid, cues.

Right Hemisphere Dominance for Visuospatial Attention

Our results reveal hemispheric asymmetry for two features: (1) the right hemisphere stimulation facilitated responses to targets in both hemifields, whereas TMS over the left FEF facilitated responses to contralateral targets only; (2) TMS applied over the right FEF increased the cost of invalid cueing. This asymmetry is consistent with the well-documented right hemisphere dominance for visuospatial abilities. Persistent hemineglect can result from right, but not left, frontal lobe lesions (e.g., Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Guarriglia, Padovani, Pantano, & Pizzamiglio, 1993; Heilman & Valenstein, 1972). A recent event-related fMRI study has shown also that while the activation in the region of the left FEF was higher for contralateral shifts, the equivalent region in the right hemisphere gave equal response for left- and right-sided shifts of attention (Perry & Zeki, 2000). This, together with studies of visual perception in split brain patients (Mangun et al., 1994), suggests that the right hemisphere mediates attention to both sides of the visual space, whereas the left hemisphere is able to mediate attention to the contralateral side of the visual space only (Mesulam, 1981, 1999; Mangun & Hillyard, 1990; Heilman & Van Den Abell, 1980). Consistent with this view, TMS over the right FEF might enhance attention across the entire extra-personal space, whereas TMS over the left FEF would enhance attention within the right hemispace only.

Studies of patients with parietal lesions have shown that the right hemisphere is important for the disengagement and reorienting of visuospatial attention (Posner et al., 1984). The increase in cost of invalid cueing suggests that stimulation over the right FEF accentuates the misleading effect of the cue and impairs subsequent disengagement and shift of attention. In addition, brain imaging studies suggest that the left and right FEF are not in the same "activation state" during covert orienting tasks similar to ours (Perry & Zeki, 2000; Nobre et al., 1997; Corbetta et al., 1993). This might explain why the left and right FEF showed a different response to TMS. Such interaction between the attentional context and the effect of TMS has already been described for the visual cortex: Direction of attention prior to target onset could counteract the negative effect of TMS on contrast discrimination in the corresponding spatial field (Brown, Wassermann, Ungerleider, & Kastner, 2000).

Origin of the Facilitating Effect of TMS over the FEF

Although the most common effect of TMS is disruptive, TMS can also enhance performance (e.g., Hilgetag, Théoret, & Pascual-Leone, 2001; Oliveri et al., 1999; Töpper, Ottaghy, Rugmann, Oth, & Uber, 1998; Seyal, Siddiqui, & Hundal, 1997). A possible mechanism for such facilitation is that TMS increases the cortical excitability and/or functional connectivity of the stimulated neuronal network. It has been demonstrated indeed that TMS can increase excitability of the motor cortex (Strafella & Paus, 2001; Rothwell, 1999). We discuss now this issue in regard to the facilitation of visuospatial performance observed after stimulation over the FEF.

FEF Characteristics and TMS: Influence on Visual Detection

Electrical recordings in the FEF have shown not only oculomotor but also visual responses, both in monkeys (reviewed in Schall, 1997) and in humans (Blanke et al., 1999). When investigating further its visual function in nonhuman primates, the FEF has been described as a saliency map, that is, a representation of the extrapersonal visual space in which the locations of potential targets are registered (reviewed in Schall & Bichot, 1998). A recent study has demonstrated that subthreshold microstimulation of monkey FEF neurons applied during a 100-msec period "before" the dimming of a precued target improved significantly subsequent visual detection (Moore & Fallah, 2001). This was true only when the target was in the motor field of the stimulated neuron. The authors suggested that electrical stimulation facilitated the visual signaling of objects inside the motor field and thus increased their salience. TMS over the FEF might have similar effects at the scale of neuronal populations: It would enhance the global representational map, facilitating the detection of peripheral visual targets.

TMS might facilitate the visual processing by briefly increasing cortical excitability of FEF visual neuronal populations. In monkeys, a large number of neurons (>50%) within the FEF exhibit visual responses with a mean latency around 50 msec (Thompson, Hanes, Bichot, & Schall, 1996; Bruce et al., 1985). Therefore, TMS applied 53 msec before the target in our experiment, that is about 100 msec before the mean visual response, could probably have an effect on the majority of visual neurons. TMS applied 67 msec after the target may have been too late to influence significantly the visual response. Thompson and Schall (1999) provided further evidence that the FEF is one site of early visual processing. They described a population of FEF neurons whose activity predicted the detection of a visual target in a masking paradigm. When applied over the FEF before target onset, TMS might lower the "detection threshold" of those neurons and thereby facilitate visual processing and speed up the response. A lower contralateral bias for right than for left FEF visual responses could account for the asymmetry of the TMS effect.

Specificity of the FEF in the Origin of Facilitation

One other possibility is that the observed facilitation was due to other areas, either in the vicinity of or connected with the FEF. We cannot rule out that, even using a relatively focal coil, the stimulation centered over the FEF does induce current in other proximal areas such as the dorsal premotor cortex. Visuomotor neurons have been found in the homologue of this region in monkeys (see, for instance, the review by Boussaoud & Bremmer, 1999). Whether a low-intensity stimulation could influence those neurons merits further investigation. Yet, the numerous lines of evidence showing that the FEF is involved in both saccadic preparation and visuospatial attention, as well as the rapid decay of the cerebral current elicited by TMS, lead us to believe that the observed effect arises from the FEF neuronal populations. To address this issue further, we analyzed the visuospatial attention performance of subjects in whom stimulation over the probabilistic location of the FEF did not produce any disruptive effect on the oculomotor task (data not showed). These subjects were not included in the main analysis since the lack of oculomotor effect was an indication that we were not stimulating the FEF neuronal populations. In this group of subjects, we did not observe any facilitation in the visuospatial task. This indicates that the effect we see in the groups reported here is specific to the stimulation of the FEF, and not to adjacent brain areas.

TMS could also facilitate visual processing indirectly by modulating cortico-cortical connectivity. One possibility is that TMS over the FEF acts on the superior colliculus or on visual areas, both densely connected with the FEF and involved in visuospatial perception (Cavada & Goldman-Rakic, 1989). TMS would therefore influence the top-down control pathway (Luck & Ford, 1998). In humans, a combined TMS/PET study demonstrated bilateral connections of the left FEF with a region located in the posterior part of the intraparietal sulcus, in the superior parietal lobule (Paus et al., 1997). Brain imaging studies have reported that covert visuospatial attention tasks activate a site close to this region (e.g., Corbetta et al., 1993). Thus, a possibility exists that the observed effect of TMS reflects a modulation of the fronto-parietal circuit that includes this region of the parietal cortex and the FEF.

A second indirect effect could be that the facilitation arises from a dishinbition of other competing circuits. Recently, Hilgetag et al. (2001) reported that after repetitive TMS over the right parietal cortex, subjects were better at detecting ipsilateral targets. The authors argued that this facilitation was due to a disruption of the inhibition exerted by the right over the left parietal cortex, in line with interhemispheric inhibition models (e.g., Kinsbourne, 1977). We used single-pulse TMS, which is unlikely to impair cortical function to the same degree as repetitive TMS, and we observed a facilitation for contralateral targets.

Facilitation is Not Due to Peripheral Sensation nor to Motor Pathway Excitation

One can argue that the somatosensory stimulation of the scalp accompanying a TMS pulse could induce intersensory facilitation resulting in shorter RTs. Terao et al. (1997) reported such nonspecific TMS effect during simple RT task. Fernandez-Duque and Posner (1997) observed that an auditory warning signal presented before the cue can facilitate visuospatial tasks similar to ours. This phenomenon was due to alerting and was distinct from orienting mechanisms. We used white noise to mask the sound of the TMS pulses that might have acted as a warning signal. It is still possible that somatosensory stimulation provided such warning signal. We can, however, rule out intersensory facilitation or alerting in the present study for several reasons. First, the stimulation of the anterior temporal cortex, yielding the same subjective sensation and therefore having the same alerting effect, never produced facilitation. Second, since the cue–target interval was constant, cues act themselves as visual warning signals. There would be probably little summation with warning from another modality (Fernandez-Duque & Posner, 1997 Experiment 3). Third, if peripheral effects were to be responsible for speeded responses, we would have expected these effects to be either bilateral or ipsilateral (i.e., orienting towards the side of the stimulation), and most probably present for all cueing conditions. In contrast, we observed a stronger contralateral effect.

In addition, the facilitation was not observed for invalid trials in the right FEF stimulation.

Another possibility would be that the stimulation of the FEF "spreads" into the motor cortex, and thereby facilitates the manual response. Yet, because responses were always made with the right hand, we would have expected a stronger effect of the left FEF stimulation and for all conditions, independently of the target location. This was not the case.

Methodological Issues

We considered that the coil was positioned over the FEF only if single pulses delayed saccades towards the contralateral visual field more than saccades towards the ipsilateral visual field. For each stimulated hemisphere, only half of subjects met this criterion. Several explanations might account for this rather low proportion. (1) In some subjects, the region targeted using anatomical considerations might not correspond to the functional FEF. Indeed, meta-analysis of PET studies or individual analysis in fMRI oculomotor experiments showed significant variability of the location of the main frontal oculomotor region (Lobel et al., 2001; Luna et al., 1998; Paus, 1996). (2) The TMS intensity might have been insufficient to produce detectable effects. For instance, Priori et al. (1993) have shown a relationship between TMS intensity and the latency of visually or auditory-cued saccades; and in some subjects, they had to increase stimulation intensity up to 80% of the maximum stimulator output to observe significant delay. Thickbroom et al. (1996) and Zangemeister et al. (1995) also used higher intensities than those employed in the present study. (3) Previous studies (Thickbroom et al., 1996; Priori et al., 1993), which showed that TMS over the frontal cortex increased latencies for contralateral saccades, did not provide clear-cut results for ipsilateral saccades. Thus, TMS over the FEF might have a bilateral effect, as we observed in the group analysis and for three subjects in individual analysis. This issue deserves further investigation.

Conclusion: TMS, FEF, and Overt versus Covert Shifts of Attention

Our results indicate that single-pulse TMS delivered over the same site can have different effects depending on the behavioral context. We observed that TMS over the FEF had a disruptive effect on oculomotor preparation and a facilitatory effect on detection of visual, stimuli. This facilitation is consistent with the saliency map model of the FEF that has been developed to account for results gathered in nonhuman primates. In this framework, the role of the FEF might be to "highlight" specific parts of a spatial map and thereby facilitate sensory processing. Moreover, in the case of the right hemisphere stimulation, we observed differential effect depending on the validity of the cue and resulting in increased cost. The latter observation suggests that TMS applied over the right FEF interferes with the disengagement of visuospatial attention. The fact that there is both facilitation of visual detection and impairment of attentional orienting can be explained by the dual role of the FEF in visuospatial perception and visuospatial orientation. TMS over this region might at the same time (1) increase the excitability of the saliency map, thereby facilitating visual detection, and (2) disrupt the disengagement of the spatial attention network in a similar way it disrupts preparation of saccadic eye movements.

METHODS

The study conformed to the Declaration of Helsinki and was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital. All subjects were normal healthy volunteers (13 men and 4 women, age 20–35, all right-handed) and gave their informed consent before starting the study.

Transcranial Magnetic Stimulation

We used a figure-8 coil (Magstim, each wing 7 cm, connected via a BiStim module). For each subject, the resting motor threshold was assessed as the intensity necessary to elicit a motor twitch in muscles of the contralateral hand in 5 out of 10 trials. For the FEF stimulation intensity was set 5% above this threshold. The average stimulation intensity across subjects was 51% (*SD* 8.5) of the maximum stimulator output. None of subjects reported any kind of discomfort. Single pulses were applied at an averaged rate of 1 every 5 sec. In order to protect their hearing from the noise caused by TMS, subjects had foam insert earphones during the experiment. During the visuospatial attention task, white noise was delivered through the earphones in order to mask the auditory clicks.

Coil Positioning

FEF location was marked on individual anatomical MRI using averaged Talairach coordinates: left FEF = −32/−2/46; right FEF = 31/−2/47 (Paus, 1996). In all subjects, this site lied in the precentral sulcus near the junction with the superior frontal sulcus (see Introduction). Frameless stereotaxy (Brainsight, Rogue Research, Inc., Montreal, Canada; http://www.rogue-research.com) was used to position the center of the coil (junction of the wings) over this site in each individual (Paus, 1999). The coil was oriented so that the induced current flowed in the direction of the precentral sulcus from lateral to medial. Subject's head was restrained with a chin and forehead support attached to the same device as the coil holder.

Functional Marker: Oculomotor Task

In order to ensure that we were indeed stimulating the FEF, single-pulse TMS was applied over the putative FEF in each subjects during an oculomotor task. In this task, subjects sat in a darkened room, 57 cm from a monitor displaying a central fixation point and two peripheral boxes 7° apart from fixation (1.5 × 1.5° rectangles). The task was to make an ocular saccade either toward the left or right box, depending on the block, in response to an auditory cue. After short habituation practice, the saccadic latency was evaluated on a sample of 20 saccades using on-line electrooculography (EOG, separately for leftwards and rightwards saccades). In a subsequent block of 51 saccades, TMS was applied randomly across trials 50 msec before predicted onset of saccade, as derived from saccadic latencies obtained in the 20 no-TMS trials administered beforehand. Thirty trials with TMS were intermixed with 21 trials without TMS.

Eye movements were recorded with EOG using a dedicated system compatible with TMS (Virtanen, Ruohonen, Naatanen, & Ilmomieni, 1999; see Paus, Sipila, & Strafella, 2001 for a discussion about potential artifacts). One hundred microseconds before delivering the TMS pulse, a trigger signal was sent to the amplifier to shut it down and to pin the output for 2.5 msec. This prevented any major artifact or drift in the signal. The amplifier bandwidth was 0.1–500 Hz and the signal was sampled at 1.45 kHz. Saccadic latencies were computed off-line. Data were first highpass-filtered (MATLAB 5.1, cutoff frequency 5 Hz; Hamming window 50 msec) in order to eliminate any low-frequency drift in the signal, and were lowpass-filtered (cutoff 55 Hz) in order to remove high-frequency artifacts. Saccadic latencies were determined trial by trial as the time interval between the onset of beep (recorded via a TTL pulse) and the onset of the saccades (determined as the first point of a deflection corresponding to a saccade). Trials in which saccade onset occurred before the TMS pulse and trials contaminated with eye blink were discarded.

Previous studies have shown that TMS applied over the FEF 50 msec before the onset of an auditory-cued saccade delays saccades towards the hemifield contralateral to the site of stimulation (Thickbroom et al., 1996). Accordingly, we considered as a functional marker of stimulating the FEF any increase in latencies for contralateral saccades. This was tested in each individual using Wilcoxon statistics. If latency increased for both directions of saccades, we consider the site as the FEF only if this increase was significantly higher for contralateral than for ipsilateral saccades. We selected subjects and sites of stimulation exhibiting this pattern (see Figure 2). During the same session, their performance in the visuospatial attention task was assessed when stimulating exactly the same sites.

Visuospatial Attention Task (Figure 1)

At the start of each trial, the subject fixated a central dot. After 530 msec, the dot was replaced by a central cue. This cue, sustaining 1° of visual angle, was either an arrow directed to the left or to the right (informative cues), or a diamond (uninformative or neutral cue). It remained on the screen until the end of the trial. The target appeared 400 msec after the cue, 7° left or right. This target was a green isoluminant 0.9 × 2 or 0.9 × 2.8° rectangle which was presented for 53 msec (four monitor refreshing frames). All stimuli were displayed on a monitor with gray background, in a semidarkened room. The task was to discriminate the height of the stimulus bars and to make a speeded two-choice right-hand response (one key for long bars, another for short bars). Short bars were much less frequent (11%) and were not taken into account in the RTs analysis. The purpose of a discrimination task was to avoid automatic anticipatory responses. The purpose of keeping the same timing was to maintain constant time relation between cue–TMS and TMS–targets intervals. Subjects were instructed to take advantage of the informative cues since, most of the time, it would predict the location of the target. The cue was neutral in 25% of trials, valid in 65%, and invalid in 10%. Targets were equally distributed between both visual fields. TMS was applied randomly across trials either 53 msec before the target, or 67 msec after. For each of the two intervals, 15 trials per condition (Cue validity × Target's hemifield) were collected for each hemisphere stimulated. For each site of stimulation each subject underwent three blocks of 168 trials. On average, there was one trial with TMS for two trials without. White noise (85 dB) was played through the insert earphones in order to mask the TMS-induced "click."

We recorded EOG continuously with 2.5 msec shutoff of the amplifier at the time of TMS pulses, as described above. The recordings were analyzed off-line, after appropriate filtering, on a trial-by-trial basis. Using a Matlab dedicated program and individuals calibration files, we identified any trial in which an eye movement larger or equal to 1° had occurred in between the cue onset and 400 msec after the target. We chose this time window in order to detect saccades that could have occurred in response to the cue, in response to the TMS pulse or in response to the target. By this process, we also identified trials contaminated by blinks.

Control Group

The length of the experiment did not allow testing several brain sites within one session in the same subject. Therefore, the control site of stimulation was tested in a separate control group (5 men, 1 woman, age 23–33, all right-handed) performing only the visuospatial attention task. TMS was applied either 53 msec before or

67 msec after the target. The coil was positioned over the middle temporal lobe (mean coordinates in Talairach space: left hemisphere = −67/−16/8; right = 67/−16/8). This location was selected for its low probability of modulating visuospatial functions and because the TMS yielded similar subjective peripheral sensations at the scalp.

Analysis

Trials with eye blinks, saccades, anticipatory responses (RT < 100 msec), or no response (RT > 1000 msec) were discarded (0–20% of trials, mean 5.9%, *SD* 6.3). The error rate was calculated on the remaining trials. For each subject, a global scaling, equalizing mean RT for all sessions, was applied in order to correct for practice (time) effects. Then, the logarithms of medians RT were submitted to a repeated-measure analysis of variance in order to assess the main effects of TMS (intraindividual factors: cue, visual field of target, TMS). In order to compare the effect of TMS over different sites, median RTs in TMS trials were normalized by the RT in the corresponding no-TMS condition. The logarithm of those numbers was submitted to a repeated-measure analysis of variance with cue and target side (ipsi- or contralateral to the stimulation), as intrasubjects factors and TMS site as intersubjects factor. Post hoc tests were performed using Newmann–Keuls procedure to test the probability of the difference in each couple of means, taking into account the number of samples. This procedure minimizes Type I errors due to multiple comparisons.

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