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Transcranial magnetic stimulation of the human frontal eye field facilitates visual awareness

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Abstract

What are the brain mechanisms allowing a stimulus to enter our awareness? Some theories suggest that this process engages resources overlapping with those required for action control, but experimental support for these ideas is still required. Here, we investigated whether the human frontal eye field (FEF), an area known to control eye movements, is involved in visual awareness. Volunteers participated in a backward masking task in which they were able to detect a target in a small proportion of trials. We observed that a single pulse of transcranial magnetic stimulation applied over the FEF shortly before the target's onset facilitated visual sensitivity; subjects were able to detect an otherwise subliminal object. These results show that modulating the neuronal activity of the FEF can enhance visual detection, thereby yielding new insights into the neural basis of visual awareness.

Introduction

The frontal eye field (FEF) is defined as the main cortical region devoted to the control of eye movements. In nonhuman primates, its role in visual processing is equally compelling, however (Latto & Cowey, 1971). The FEF possesses bidirectional connections with various visual areas both in the dorsal and ventral stream (Felleman & Van Essen, 1991; Schall, 1997), and visual responses occur in the FEF as early as 55 ms after the stimulus onset (Schall, 1997; Schmolesky *et al*., 1998).

Two important studies have described a direct relationship between the FEF neuronal activity and the conscious detection of visual stimuli. Moore & Fallah (2001) observed that microstimulation of FEF neurons, using a current below that needed to elicit an eye movement, significantly lowers the threshold for detecting a luminance change. Thompson & Schall (1999) showed that the neuronal activity in FEF neurons predicts whether the monkey detects a target that is masked by a subsequent stimulus.

In human subjects the visual function of the FEF is less well documented. Early (70–100 ms) visual evoked activity has been observed over the putative FEF using intracranial (Blanke *et al*., 1999) or scalp potential recordings (Foxe & Simpson, 2002). Brain imaging studies also suggest that activity within the FEF correlates with conscious visual detection or discrimination (Shulman *et al*., 2001).

Our goal is to investigate further the involvement of the human FEF in visual processing, and more specifically in visual awareness. One possible methodology is to manipulate the activity of FEF neuronal populations and observe whether conscious detection is altered. Transcranial magnetic stimulation (TMS) can be used in human volunteers to modulate cortical activity in a time- and space-limited manner and, in turn, can impair or facilitate behaviour related to the targetted region. When applied over the human FEF, TMS interferes with oculomotor behaviour, rather than eliciting eye movement (Müri *et al*., 1991; Thickbroom *et al*., 1996). In a previous study, we applied single-pulse TMS over the FEF during a visuospatial attention paradigm (Grosbras & Paus, 2002). In this task, subjects had to respond manually to a peripheral target the location of which could be precued. We observed that, when applied shortly before the visual target, TMS reduced reaction times regardless of precueing. We hypothesized that TMS applied over the FEF had facilitated conscious visual detection. To test this hypothesis further and to answer questions regarding the involvement of the human FEF in visual awareness, we designed a new study in which we could measure directly an improvement in visual detection. We used a backward masking paradigm in which the visibility of a visual stimulus (the target) was rendered unreliable by the subsequent presentation of another stimulus (the mask; Breitmeyer, 1984; Enns & Di Lollo, 2000; see Fig. 1). In some trials, we stimulated the FEF before the presentation of the visual target. We predicted that, if the FEF is involved in visual awareness, that is in visual perception with consciousness, than the TMS-induced change in FEF neuronal activity should facilitate sensitivity to a subsequent visual stimulus.

Materials and methods

Subjects

Twenty-two subjects [seven females, age 23–41 years (mean 29 years), all right-handed] gave informed consent and participated in the study. None of them had any history of neurological or psychiatric disorders; all had normal or corrected-to-normal visual acuity. The study was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital.

TMS parameters and location

The TMS was delivered with a Magstim 200 stimulator and a figure-of-eight coil (internal wing diameter 70 mm, connected through a Bistim module). Earplugs attenuated the click generated by the coil discharge, protecting the subject's hearing and diminishing the alerting effect.

With the coil positioned over the motor cortex, we first determined the resting motor threshold as the minimal intensity necessary to elicit

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a visible twitch in the hand muscle. We set the stimulation intensity 10% above this value for the rest of the experiment. The stimulation intensity ranged from 36 to 58% (mean, 50%) of the maximum stimulator output.

We localized the FEF on the anatomical magnetic resonance image (MRI) considering the intersection between the precentral sulcus and superior frontal sulcus as an anatomical landmark [mm coordinates in standard stereotaxic space (Talairach & Tournoux, 1988; left hemisphere, −32, −2, 46; right, 31, −2, 47; Paus, 1996). We used frameless stereotaxy (Brainsight, http://www.rogue-research.com) to register the MRI to the head of the subject and position the coil over the putative FEF. The coil was orientated so that the induced current flowed in the direction of the precentral sulcus from lateral to medial. Head movements were restricted using a chin and forehead rest attached to the same support as the arm holding the TMS coil.

As a control, we stimulated a region in the anterior temporal lobe (coordinates in standard stereotaxic space; left hemisphere, −67, −16, 8; right, 67, −16, 8). The orientation of the coil was adjusted on an individual basis to make sure that the single pulses elicited similar peripheral sensation to stimulation over the FEF. We did not observe a facial twitch with any of the stimulation sites. The order of stimulation sites was counterbalanced across subjects.

Because of the length of the experiment, only two sites of stimulation (FEF and control) could be tested during one session. The left and right hemispheres were therefore stimulated in different groups of subjects.

Functional targeting of the FEF

Before testing the subjects in the visual detection task, we applied TMS over the targeted location during an oculomotor task in order to verify that the stimulation at the FEF site, and with this intensity, interfered with the FEF functioning. It has been demonstrated previously that TMS applied during the oculomotor preparation, just before the saccade onset, increases the saccade latency (Thickbroom *et al*., 1996). Subjects were asked to move the eyes from the central fixation point towards a target, located at 7° eccentricity, in response to an audio signal. For each individual, after a practice session allowing the latencies to stabilized, we measured the median latency in a sample of 20 saccades. We then delivered single-pulse TMS (50 ms) before the expected onset of saccades (i.e. during the saccadic preparation) in 28 out of 56 trials in a pseudorandom order. This procedure was repeated separately for leftwards and rightwards saccades.

Eye movements were recorded with electrooculography (EOG) using a dedicated system compatible with TMS (Virtanen *et al*., 1999). One hundred microseconds before delivering the TMS pulse a trigger signal was sent to the amplifier to pin its output and hold it for 2.5 ms. This prevented any major artifact or drift in the signal because of a TMS pulse. The amplifier bandwidth was 0.1–500 Hz and the signal was sampled at 1.45 kHz. Latencies between the audio signal and the onset of the subsequent saccade were determined offline trial-by-trial using a dedicated program written in Matlab (The Mathworks, Inc.). Trials in which saccade onset occurred before the TMS pulse and trials contaminated with eye-blinks were discarded. A significant increase in latencies for contraversive saccades, as tested by the Wilcoxon rank test, was considered as indicating a successful targeting of the FEF. Only the 16 out of 22 subjects showing this effect were selected to test whether TMS applied over the same location would change visual awareness.

Visual detection task and stimulus presentation

The visual detection task was carried out just after the oculomotor with the subject and coil at the same position. The TMS intensity was kept the same, i.e. 110% of the motor threshold. A monitor (CRT Multisync 19-inch, 75 Hz) was positioned 60 cm from the subject's eyes. The screen background was grey with a luminance of 3.1 cd/cm^2. The target stimulus consisted of a dim green square (12.2 cd/cm^2) sustaining 1 × 1° of visual angle. It was presented 5° from the fixation point at one out of four possible locations: left lower or upper quadrant and right lower or upper quadrant. The mask consisted of eight bright white squares (74.3 cd/cm^2) arranged on a 5° radius circle. Four of these squares were at the possible target locations. Each trial started with the appearance of a central fixation point. After 600–800 ms, the target stimulus appeared for 13.3 ms (one refresh frame of the monitor) immediately followed by the presentation of the mask for 40 ms. In 25% of the trials, no target was presented. The subjects responded by a keypress in a three-choice manner: no target; left target; right target. The succession of trials was self-paced, allowing subjects to rest and blink in between trials. The stimulus onset asynchrony (SOA), defined as the delay between target's onset and mask's onset, could be either 13.3, 26.6, 40 or 53.3 ms (1, 2, 3, or 4 refresh frames of the monitor). For this type of backward masking, the strength of masking depends on the SOA, being greater for short SOAs (see Fig. 1b). At the beginning of the study, each subject had undergone a 15-min training session in which all four SOAs were intermixed. The performance assessed on the basis of 192 trials at the end of the training session was used to select two or three adjacent SOAs; the shortest SOA led to at least 17% correct detection and the longest SOA to less than 100% detection. This procedure was implemented to avoid floor and ceiling effects and to study TMS effects at similar performance levels across subjects. In

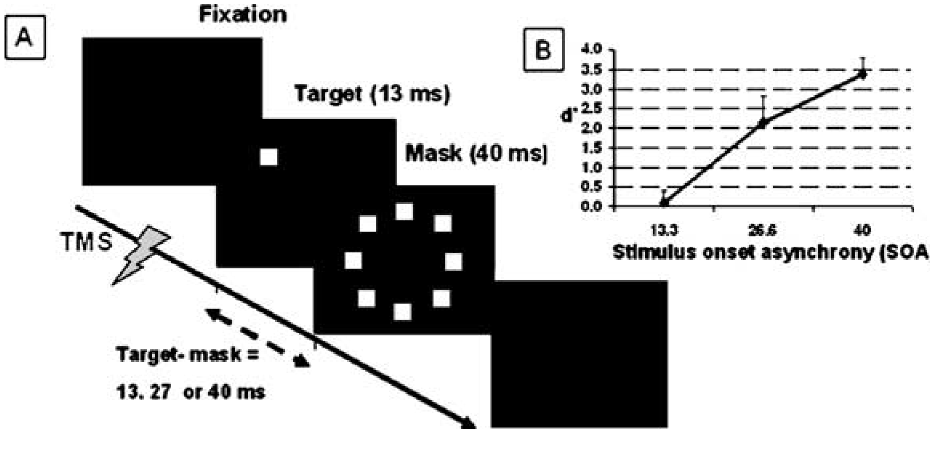

FIG. 1. (A) Stimuli and task design. The targets could appear at the location of one of the elements constituting the mask, in the left or right hemifield but not at the upper or lower positions (12 o'clock and 6 o'clock). (B) Performance for different SOAs obtained in 20 subjects in a preliminary experiment (mean + SEM).

the group we report here, participants were tested with either 13.3 and 26.6 ms SOA; 26.6 and 40 ms SOA; or 13.3, 26.6 and 40 ms SOA. They performed three blocks of 60 or 80 trials (depending on the number of SOAs tested). Each block lasted for about 5 min. The TMS was delivered 40 ms before the onset of the target randomly in two thirds of the trials. Altogether we collected 24 trials per condition (TMS-FEF, TMS-control or No-TMS; target in the left or right visual field).

Data analysis

During the visual detection task, eye movements were recorded with EOG (see above) and trials with eye movements or blinks occurring in a window of −500 to +400 ms around the target were discarded. Velocity superior to 100 °/s and amplitude superior to 1°, according to a calibration file acquired just before the experiment, were taken as criterion to define an eye movement or blink. The proportion of such trials varied across subjects from 0 to 17% and was not different across TMS conditions.

Single trials were classified into: correct detection; correct rejection; omission (miss); false alarm (yes response in a trial without target); and error (yes response but for the incorrect hemifield). The proportion of trials in each category was computed separately for targets presented in the left and right hemifield. We first computed the detectability index, d', from the percentages of hits and false alarms [p(hits) and p(fa), respectively,], according to signal detection theory, i.e.

$$d' = z[p(\text{hit})] - z[p(\text{fa})]$$

where z is the inverse of the centred normal distribution. For this measure, error trials were discarded. We also analysed the percentage of false alarms and errors, and response bias. Those measures were entered in a repeated measure analysis of variance, with target's hemifield (contralateral, ipsilateral) and TMS condition (TMS-FEF, TMS-control and No-TMS) as within-subject variables. Specific contrasts were tested with planned comparisons within this design using the software Statistica (Statsoft Inc.).

Results

We first considered the results for the shortest SOA tested for each subject (13.3 ms for five subjects and 26.6 ms for the remaining 11 subjects). TMS had a highly significant main effect ($F_{2,28} = 10.56$, $P < 0.0004$) on d'. This reflected an increase in d' in trials with TMS applied over the FEF, as compared with trials without TMS or with TMS applied over the control site. The interaction between TMS condition and hemisphere stimulated was not significant ($F_{2,28} = 0.62$, $P > 0.54$), indicating that the effect of TMS on d' was similar after the left and right FEF stimulation. The three-way interaction between TMS condition, Hemisphere and Hemifield was not statistically significant ($F_{2,28} = 2.22$, $P < 0.127$), but suggested a tendency for different lateralization of the effect for left vs. right hemisphere simulation. Indeed, planned comparisons showed that the increase in d' after stimulation over the right FEF was significant for visual targets presented both in the left and the right hemifield ($F_{1,13} = 4.025$, $P < 0.0066$; and $F_{1,13} = 11.74$, $P < 0.0045$, respectively), whereas after the stimulation applied over the left FEF, the effect occurred only for contralateral ($F_{1,13} = 19.48$, $P < 0.0007$), and not ipsilateral targets ($F_{1,13} = 0.31$, $P > 0.58$; Fig. 2). There was no correlation between d' and TMS intensity, or subject's age or gender.

In a separate analysis including the 13 subjects for whom we had data for two SOAs without a ceiling effect, we tested the effect of TMS on d' as a function of SOA. The interaction between TMS and SOA was not significant ($F_{2,22} = 1.26$, $P > 0.30$), indicating that TMS had the same effect on short and long SOAs. Therefore the effect was independent of the delay between TMS and mask.

There was no significant effect on error rate. There was a tendency for higher number of false alarms after TMS over the control site, but not over the FEF. There was no effect of TMS on response bias or criterion.

To explore further the effect of TMS on d', we tested a subset of three subjects while varying the delay between the TMS pulse and the target onset. We observed an increase in d' only when applying TMS between 100 and 40 ms before the target (Fig. 3).

Discussion

We observed that a single pulse of TMS applied over the frontal eye field increases the probability of detecting a target presented 40 ms later. This effect is highly significant and found in 13/16 (81%) subjects. Stimulating a control region did not alter performance; thus, it is unlikely that the auditory and somatosensory effects of the TMS would contribute to the increase in sensitivity. The change in d' was not

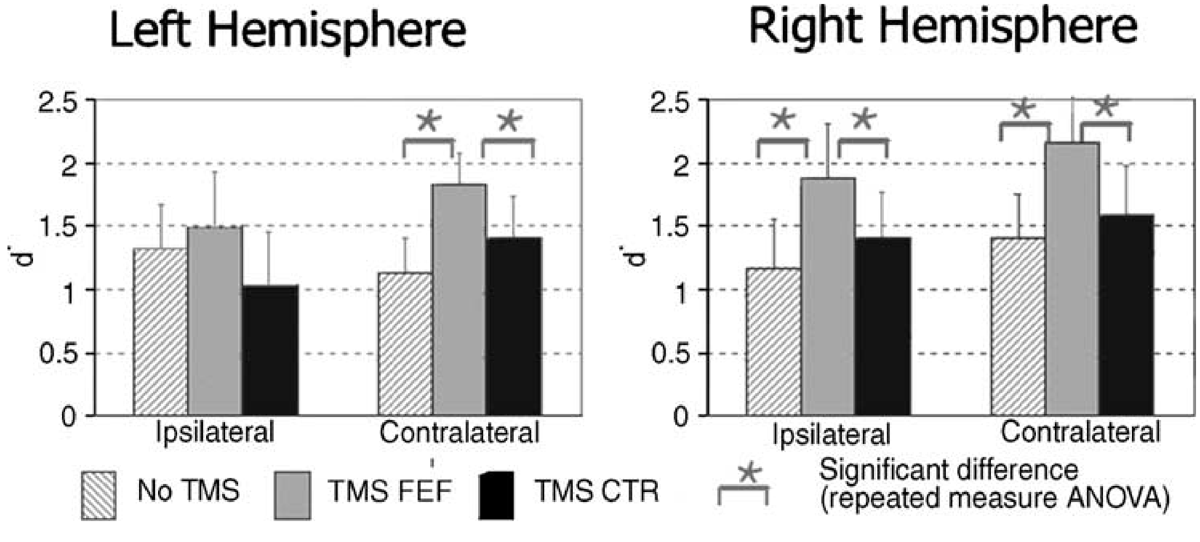

FIG. 2. Results. Bars represent d' (mean ± SEM) calculated separately for targets in the hemifield ipsilateral and contralateral to the site of stimulation and for trials without TMS (No TMS), with TMS applied over the FEF (TMS FEF) and with TMS applied over the control site (TMS CTR). Asterisks represent significant difference ($P < 0.05$) as tested with planed comparison in a repeated-measure ANOVA.

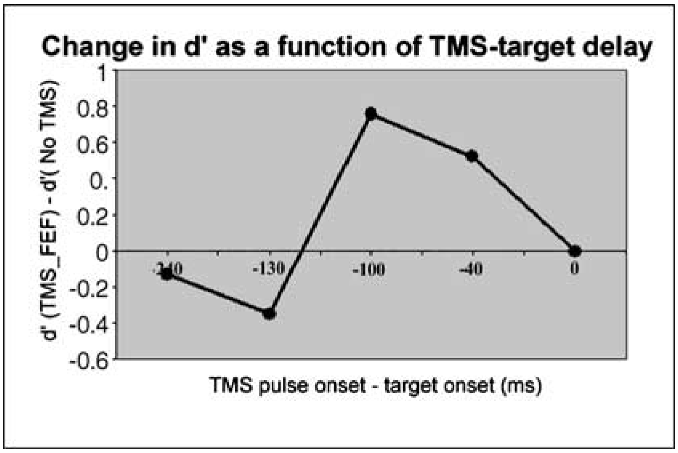

FIG. 3. The change in d' was measured as the difference between trials with TMS applied over the FEF minus trials without TMS for various delays between the TMS pulse and the target onset (see Results).

accompanied by any change in response bias. We suggest that TMS applied over the FEF in a narrow time-window increases the sensitivity of the visual processing, and thereby allows the detection of an otherwise subliminal visual stimulus.

One possible mechanism accounting for the facilitation of awareness (that is, conscious visual detection) is that TMS applied over the FEF modulates the visual system so that a stimulus presented just after the TMS pulse elicits a stronger neuronal response. That single-pulse TMS can increase cortical excitability has been demonstrated consistently in the motor system. The muscle response induced by a TMS pulse applied over the motor cortex is enhanced if the pulse is delivered 12–50 ms after a subthreshold pulse or up to 100 ms after a suprathreshold pulse (Valls-Sole *et al*., 1992). In nonhuman primates, several researchers have applied electrical microstimulation in order to manipulate neuronal activity and observed correlations with the behavioural response to sensory events. For instance, Salzman, Britten *et al*. (1990) stimulated MT neurons (sensitive to motion) while a monkey had to determine the direction of motion of a random moving dots pattern; they observed an improvement in performance especially when the visual stimulus provided little directional information. Moore & Fallah (2001) demonstrated that a train of electrical stimulation, with a current intensity too low to elicit an eye movement, applied to FEF visuomotor neurons during the 100 m period preceding the dimming of a visual target significantly decreased the threshold for detecting the luminance change; this result is strongly consistent with our observations.

The hypothesis that the amount of neural activity induced by a stimulus determines whether or not a stimulus reaches awareness is compatible with 'accrual decision-making' models. These models propose that the accumulation of a signal up to a certain threshold is necessary for making a decision, motor or perceptual. If the background activity is moved closer to threshold, any incoming signal can reach threshold more rapidly (Hanes & Schall, 1995; Carpenter, 1999; Gold & Shadlen, 2001). This hypothesis is supported by observations that stimuli of which we are not conscious still induce cortical activity in brain areas known to be involved in their processing (Macknik & Livingstone, 1998; Lumer & Rees, 1999; Dehaene *et al*., 2001; Vuilleumier *et al*., 2001). This suggests that the difference between stimuli that reach awareness, i.e. that are consciously detected, and those that do not might depend upon the degree of activation of the particular network that processes the stimulus rather than on the recruitment of structures specific for awareness. In this context, it is conceivable that a slight change in background activity can change the probability that a sensory stimulus of a given energy enters consciousness. Having that in mind, it is possible that stimulating over the FEF 'preactivates' the visual system so that the signal evoked by the subsequent target is more likely to elicit awareness. The increase in sensitivity was observed when TMS was applied 40 ms before the target and additional data obtained in three subjects suggest that, to be effective, the TMS had to occur between 100 and 40 ms before the visual target, that is about 100–200 ms before the visual signal reached the FEF (Schmolesky *et al*., 1998; Foxe & Simpson, 2002). This timing is in agreement with findings in the motor system: intracortical facilitation has been demonstrated as being maximal about 200 ms after a somatosensory stimulation (Kobayashi *et al*., 2003).

This also points towards an important methodological issue regarding TMS studies: depending on the exact timing of the stimulation relative to the engagement of the stimulated region in the task of interest, TMS can have either facilitatory or interfering effects. In our case, when TMS was applied over the FEF during the late phase of saccadic preparation it delayed the onset of the saccade; when applied before a masked visual target it facilitated detection. In addition, the difference between the effects of TMS on each task might be because different neuronal populations within the FEF participate in those computations.

Overall, a modulation of neuronal activity in various regions, with TMS (human studies) or intracortical microstimulation (monkey studies), has been shown to facilitate subsequent responses to incoming relevant stimuli. Our results together with those of Moore & Fallah (2001) illustrate how a modulation of FEF neuronal activity influences visual detection. They are also in accordance with electrophysiological recordings in macaque monkeys engaged in a backward masking experiment very similar to the one we used here (Thompson & Schall, 1999, 2000); in many FEF visuomotor neurons the pretarget activity (measured in terms of spike rate) is elevated slightly in trials in which the monkey detects the target. Also in humans, functional magnetic resonance imaging has revealed greater activity in the FEF when subjects are aware of a visual stimulus as compared with conditions in which they report not seeing the stimulus (Sahraie *et al*., 1997; Shulman *et al*., 2001).

Our data do not address directly the issue of local vs. distal effects; the enhancement of visual awareness might occur directly by changing activity in FEF neuronal populations or indirectly via connections between the FEF and other visual areas. These two alternatives are not mutually exclusive. As mentioned above, the neuronal activity within the FEF is important for awareness; the greater the activity, the higher the probability of conscious detection (Thompson & Schall, 1999; Shulman *et al*., 2001; Schall, 2002). By contrast, the position of the FEF in the visual hierarchy suggests that it can influence the activity in other visual areas through feed-back as well as feed-forward projections (Jouve *et al*., 1998; Barone *et al*., 2000). Recently Moore & Armstrong (2003) observed that electrical microstimulation of the monkey FEF enhances the visual-evoked response recorded in V4 neurons, suggesting that a stimulation of FEF neurons activates a network that controls the gain of visually driven signal in extrastriate visual areas. These authors underline that the enhancement observed after microstimulation is very similar in magnitude to the enhancement observed during selective attention tasks. The modulation of other visual regions sensitivity by a network including the FEF is indeed favoured by many models of visuospatial attention. In everyday life, visual awareness depends critically on selective attention; the same retinal stimulus can enter or escape our consciousness as a function of purely attentional factors (Treisman & Kanwisher, 1998). Masking effects, such as those employed in the present experiment, can also be attenuated by attentional factors (Ramachandran & Cobb, 1995; Enns

& Di Lollo, 2000). Visual detection, visual discrimination, as well as electrophysiological visual-evoked responses (Deubel & Schneider, 1996; Mangun *et al*., 1997) are enhanced if attention is directed in advance to the location where the visual target will appear. The origin of such a modulation is still unclear. A dominant hypothesis, however, is that 'higher-order' areas send signals to 'lower' visual areas, thereby providing a sensory gating and allowing a selection of the information to be processed. Such corticocortical interactions might be also important for determining awareness (Crick & Koch, 1998; Hupe *et al*., 1998; Lamme, 2001; Pascual-Leone & Walsh, 2001). The FEF, together with the superior parietal cortex, is one of the main candidates to exercise such control on vision (Corbetta *et al*., 2000; Schall, 2002). It is possible thereby that TMS applied over the FEF mimics attentional control and potentiates visual awareness in a way similar to what occurs naturally during covert shifts of attention (see also Moore & Armstrong, 2003). The relevance of the present data for the mechanism of visuospatial attention is also reflected in the hemispheric asymmetry; the right FEF stimulation enhanced awareness wherever the target was in the visual field, whereas the left FEF stimulation had an effect only for contralateral targets. This is consistent with the known right hemisphere dominance for visuospatial attention and the results from previous TMS studies (Walsh *et al*., 1999; Grosbras & Paus, 2002). Further experiments involving TMS over other visual areas will provide greater insight into the neural network involved in the enhancement of visual processing, as well as on the link between attention and awareness.

In conclusion, our data provide evidence for the role of the human FEF in visual processing and awareness. Our findings also offer experimental support for models postulating that brain structures involved in action control play also a role in perceptual decisions and consciousness (Crick & Koch, 1998; Berthoz, 1996; Gold & Shadlen, 2001).

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Abbreviations

FEF, frontal eye field; SOA, stimulus onset asynchrony; TMS, transcranial magnetic stimulation.

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