Exp Brain Res (2003) 150:290–296
DOI 10.1007/s00221-003-1470-0

RESEARCH ARTICLE

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Inhibition of return and the human frontal eye fields

Received: 26 August 2002 / Accepted: 5 March 2003 / Published online: 12 April 2003

Abstract Inhibition of return (IOR) is a bias against reorienting attention to a previously cued location. In this study, using single-pulse transcranial magnetic stimulation (TMS), we show that the human frontal eye fields (FEF) play a crucial role in the generation of IOR. When TMS was applied over the right FEF at a time interval after a visual cue but shortly before the target, IOR was modulated in the hemifield ipsilateral to the TMS such that responses to a previously cued target were no longer slower than responses to uncued targets. Control TMS over the superior parietal lobule, as well as TMS of the FEF shortly after the cue but well before the target, had no influence on IOR. We further show that the FEF is involved with visual selection as responses to targets appearing contralateral to the TMS of the FEF, but not the control site, were delayed. These results suggest that the FEF produces IOR by biasing attention and eye movements away from a previously attended location and facilitating target detection at novel locations.

Keywords Frontal eye fields (FEF) · Inhibition of return (IOR) · Saccades · Transcranial magnetic stimulation (TMS) · Reaction times · Human

Introduction

At any given instance when our eyes are open, we receive an abundance of visual information from the world. However, due to the limited spatial extent of the fovea, as well as limitations in our cognitive capacities, not all of this information can be processed extensively. To deal efficiently with all of this sensory information, our cognitive and neural systems must attend selectively to some portion of this information in space, while ignoring others. Following this orienting of attention to a spatial location, our attentional systems must rely on some mechanism to remove attention in order to inspect other relevant areas of space. One behavioral consequence of this removal of attention is the phenomenon of inhibition of return (IOR), where target detection at previously attended locations has been shown to be delayed (Posner and Cohen 1984; Posner et al. 1985; Klein 2000). The neural and psychological mechanisms that generate IOR have been a subject of much recent controversy and debate.

Since its inception, various theoretical and neural accounts of IOR have been proposed (Rafal et al. 1989; Chelazzi et al. 1995; Danziger et al. 1997; Dorris et al. 1998; Taylor and Klein 1998; Sapir et al. 1999; Dorris et al. 2002). For example, it has been suggested that IOR is a process of the attentional system through which we sample novel locations and avoid the re-inspection of already attended-to portions of objects and space (Posner and Cohen 1984; Posner et al. 1985; Klein 1988; Tipper et al. 1994; Tipper et al. 1997; Klein and MacInnes 1999). This sensory/attentional account of IOR has received recent empirical support (Lupianez et al. 1997; Handy et al. 1999; Pratt and Abrams 1999). Others, however, have suggested that IOR is simply a consequence of the activation of the oculomotor system (Rafal et al. 1989) or inhibition within it when having to suppress a reflexive glance to a peripheral visual cue (Chelazzi et al. 1995). Recently, evidence has been accumulating that both sensory-attentional as well as motor systems may be involved with the generation of IOR (Abrams and Dobkin 1994; Rafal et al. 1994; Kingstone and Pratt 1999; Taylor and Klein 2000).

The suggestions that the superior colliculus is involved with the generation of IOR (Posner et al. 1985; Sapir et al. 1999) is consistent with all of these different accounts of IOR, as it has been demonstrated that this structure is

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involved with both attention (Rafal et al. 1988) and oculomotor processes (Sparks 1989). Furthermore, since the superior colliculus contains cells sensitive to different sensory modalities, the generation of IOR in the colliculus is also consistent with recent demonstrations of IOR for tactile and auditory stimuli in addition to vision, as well as all cross-modal pairings between these modalities (Spence et al. 2000). Thus, these different accounts of IOR are not mutually exclusive, but may be different manifestations of the same underlying process. For example, a motor bias away from an already attended to location may also bias attention away from that same location (Rizzolatti et al. 1987). Recent studies have shown, in fact, that the same neural structures involved with eye movements, such as the superior colliculus and the frontal eye fields (FEF), may also be involved with attention (e.g. Kustov and Robinson 1996; Corbetta et al. 1998).

To determine the contributions of neural structures other than the superior colliculus in the generation of IOR, we examined the role of the FEF, a structure primarily involved with generating voluntary eye movements (Bruce and Goldberg 1985; Henik et al. 1994; Paus 1996; Ro et al. 1997; Luna et al. 1998; Ro et al. 1999; Rafal et al. 2000), in the generation of IOR. We reasoned that by stimulating the FEF, which is heavily connected with the superior colliculus and may be involved directly with the generation of IOR, the underlying mechanisms in the generation of IOR might be revealed. To test whether the FEF has a role in the generation of IOR, we used transcranial magnetic stimulation (TMS) to stimulate the FEF following a visual cue.

Methods

Subjects

After informed consent, following the guidelines according to the declaration of Helsinki and approval by the institutional review board of Rice University, eight subjects (four women) completed this experiment. Three additional subjects did not complete the experiment because their FEF could not be localized. All subjects were right-handed, reported having normal or corrected vision, and no history of any neurological or psychiatric disorders at the time of testing. The mean age of the eight subjects was 22.1 (range 18–35 years). They were recruited from the Rice University campus and were paid for their participation.

Apparatus

The position of the left eye was monitored using an Eye-Trac 210 (Applied Science Laboratories, Bedford, Mass., USA). Transcranial magnetic stimulation was conducted using a MES-10 stimulator (Cadwell Laboratories, Kennewick, Wash., USA). The MES-10 stimulator at maximum intensity creates a 2.2-T field (Cadwell 1990). A focal, figure-eight-shaped coil was used in this experiment. Each component of the figure-eight coil measured 4.5 cm in diameter with a maximum focus at the intersection of the two components. Although the exact volume of stimulation is not possible to determine, based on the topography of activation of finger movements with this coil, it is estimated that this coil stimulated approximately 1 cm^3 of cortex. An IBM-compatible personal computer was used to trigger the MES-10, to record the eye position, and for stimulus presentation.

Stimuli and procedure

We first localized in each subject the hand area of the right motor cortex with TMS[1]. The hand area was localized by moving the figure-eight coil around the region a few centimeters to the right of the vertex. The most anterior position where the TMS induced a contraction of the contralateral hand was defined as the motor hand area. After localizing the hand area of the motor cortex, the output intensity of the TMS device was then decreased until a contraction of the contralateral hand was no longer visible and then increased until a contraction was again visible. The latter intensity setting was defined as the motor threshold. This location served as the physiological landmark and origin for our further explorations in the prefrontal cortex. The mean TMS threshold intensity across the sessions and subjects was 56.6% (SD=8.2%, range 48–68%) of maximum output and the mean intensity used for the main experiment was 10% above this threshold value, corresponding to a mean of 62.3% (SD=9.0%, range 53–75%) of maximum output.

Following localization of the hand area of the motor cortex, we then had subjects generate endogenous saccadic eye movements in blocks of trials while stimulating over different regions of the prefrontal cortex by systematically moving the coil over nine different points on a cross with 0.5-cm separations and centered 2 cm anterior to the hand area (c.f. Ro et al. 1999). This FEF mapping procedure continued until a site was located that produced significant delays ($P<0.05$ on a one-tailed t-test) in the generation of saccadic eye movements. On average, the FEF was localized in 3.0 (range: 2–5) blocks. This mapping procedure has been described in detail elsewhere (Ro et al. 2002). Briefly, we stimulated over a given site in prefrontal cortex 50 ms before a "go" signal for an endogenous saccade towards the contralateral or ipsilateral hemifield. Endogenous saccades were prompted by directional arrowhead cues centrally displayed on a monitor. A total of 25 saccades were generated in each direction towards predefined, equidistant boxes displayed on either side of a central fixation mark. We recorded the latencies of these saccades and then performed an online analysis after each block during this mapping procedure. If no difference between contralateral and ipsilateral saccades was obtained during a given block, the coil was positioned at a site 0.5 cm away in the sagittal or coronal plane in different blocks until a site was found that produced saccadic latency asymmetries. Once a site was localized that produced significant delays in contralateral saccade direction, we defined this TMS site as being over the FEF and used this coil positioning for the main experiment. Figure 1 illustrates the location of the FEF stimulation site, across all eight subjects by plotting the effective TMS site for inducing contralateral saccade delays, with respect to the motor cortex. For this figure, the coordinates of the FEF in each subject with respect to his or her motor hand area were transformed onto the Montreal Neurological Institute template magnetic resonance imaging (MRI) scan. Since the hand area of the motor cortex of this template is known, and because we used the hand area as our functional landmark, we could then calculate on this template brain the respective FEF region in each subject to produce a statistical

[1] We only tested the right hemisphere in this study, as we were not interested in any effects of laterality, but rather only whether the human frontal eye fields are involved directly with the generation of IOR. Although in a previous study we found no differences between the left and right FEFs on the generation of endogenous saccades (Ro et al. 1997), there may be lateralization of IOR. In fact, the right hemisphere has been shown to be more involved with spatial attentional processes (Rafal 1994; Nobre et al. 1997; Driver and Mattingley 1998) and a recent functional magnetic resonance imaging (fMRI) study showed that the right, but not the left, FEF may be involved with the generation of IOR (Lepsien and Pollmann 2002). Therefore, only the right hemisphere was tested in the present study.

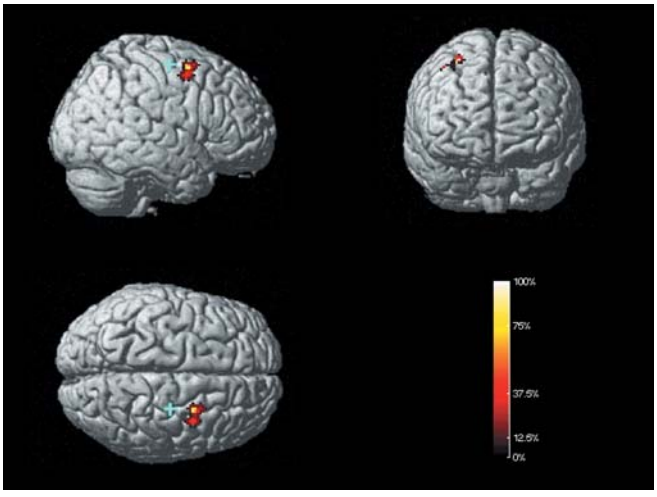

Fig. 1 The site of frontal eye field (FEF) stimulation across subjects is represented on this normalized Montreal Neurological Institute (MNI) magnetic resonance imaging (MRI) scan template. Each participant's FEF stimulation site was rendered onto this template with a 1-cm diameter circular region representing the approximate site and volume of activation by the TMS. The hand area of the motor cortex, which was used as a reference point, is depicted by the + *sign*. The scalp measurements from the hand area of the motor cortex to the FEF, taken from each subject (in millimeters), were used to plot the location of the FEF on this template with respect to the hand area in *x*, *y*, and *z* coordinates. Since the coordinate system of the MNI template is in millimeters, the distances measured on the scalp (also in millimeters) were directly translated on to this template without any scaling or normalization, which may have introduced slight offsets in the averaging. The *brighter intensities* in the frontal cortex represent greater degrees of overlap in the site of stimulation. The maximal region of overlap across the subjects was the cortex located 1.5 cm anterior and 0.3 cm lateral to the motor hand area. The figure was generated using Matlab (MathWorks, Natick, Mass., USA) and some of the functions in SPM99 (Wellcome Department of Cognitive Neurology, UCL, London, UK)

parametric map without having to obtain individual MRIs for each subject.

After the FEF mapping and for the main part of the experiment, the subjects were seated 57 cm from the computer monitor in a dimly and diffusely lit, sound-attenuated room. A small, filled, gray circle subtending 0.1° (diameter) served as the initial fixation point and was presented in the center of the monitor until the start of each trial. Two unfilled gray squares subtending 2° on each side were used as marker boxes and were present throughout the experiment. The centers of these boxes were 12° to the left and right of the fixation point. Following an inter-trial interval of 2000 ms, a non-predictive cue, the brightening of one of the two peripheral boxes, was presented. The side of the cue was randomly determined for each trial and was presented for 100 ms. In two-thirds of the trials, a TMS pulse was administered either 200 ms or 600 ms after the onset of the cue. The other one-third of the trials had no TMS and served as a further control. At 750 ms after the onset of the cue, the target, a small, white dot, subtending 0.5°, was then presented for 100 ms in the left or right box with equal probability. All stimuli were presented on a black background.

The subjects were instructed to maintain fixation, which was monitored, throughout the experiment, and to press the left button with the index finger of their right hand on a response pad when a left target appeared and the right button with the middle finger of their right hand when a right target appeared. This choice reaction time (RT) task was used since we wanted to minimize the number of trials in this experiment by excluding catch trials and the use of different cue-to-target stimulus onset asynchronies (SOAs). Subjects were asked to respond as quickly and accurately as possible using the hand ipsilateral to the TMS and to ignore the TMS pulse as best as they could when it was presented. If no response was made to the target within 750 ms following its onset, the trial timed out and moved on to the subsequent trial. Half of the subjects received TMS over the FEF for the first block, whereas the other half of the subjects first received TMS over the control site in the superior parietal lobule (SPL). The parietal cortex site was located in a homologous posterior location as the FEF stimulation site with respect to the hand area of the motor cortex. For example, if the FEF was localized to be 1.5 cm anterior to the hand area of the motor cortex, the SPL site was defined as being 1.5 cm posterior to the hand area of the motor cortex. In both TMS conditions, the coil was held with the handle of the coil oriented 90 degrees from the mid-sagittal plane.

For each TMS site, a total of 24 trials were collected for each of the 12 conditions: 2 cue (valid vs. invalid target)×2 field (contralateral vs. ipsilateral to TMS)×3 TMS delivery (no TMS baseline, 200 or 600 ms after the cue). Incorrect button responses (e.g. left button press for a right target) and responses less than or greater than 3 SD from the mean were excluded from further analysis. The remaining latencies for contralateral and ipsilateral targets in each session were then subjected to three-way, within-subject ANOVA, with cue, field, and TMS delivery as the factors for each TMS site.

Results

The overall error rate, comprising trials with incorrect button responses and responses too fast or too slow, on the speeded target localization task was only 3.6%. Because of the low error rate, these error data were not analyzed further. Eye blinks and saccadic eye movements made between 50 ms after the cue onset and until a button response was made were detected on an overall average of 12.7% of the trials. The proportions of blinks and eye movements for each of the 12 conditions were subjected to the same three-way ANOVA as the latencies. This analysis showed that the blinks and saccades were not associated with any particular condition and were distributed evenly throughout the experiment (all *Ps*>0.10). Therefore, the button-press RT data from these trials with blinks or eye movements were not discarded from the analysis.

The mean RT results for correct target localization responses are given in Table 1 and the magnitude of IOR (valid minus invalid RTs) is depicted graphically in Fig. 2. RTs were slower (i.e., IOR was present) for targets appearing at previously cued locations (valid cue conditions), except when a visual cue and target appeared in the ipsilateral hemifield to the TMS at 600 ms after the cue in the FEF stimulation condition. Note the specificity of this result with respect to the TMS site and timing. IOR was modulated only when TMS was over the FEF at a 600 ms SOA between cue and TMS pulse (TMS 150 ms before the target). When TMS was not over the FEF or when the TMS pulse arrived too early, no alterations of IOR were measured. Also present in these results was a delay in target responses when the visual target appeared in the hemifield contralateral to the stimulated FEF (see Table 1). These results suggest that the human FEF, in addition

Table 1 Mean (SD) reaction times in milliseconds, and percentage errors for each condition (*FEF* frontal eye field, *TMS* transcranial magnetic stimulation, *SPL* superior parietal lobule)

		Contralateral Targets			Ipsilateral Targets		
		No TMS	200	600	No TMS	200	600
FEF	Valid	360.8 (60.4) 4.2%	328.2 (57.5) 3.6%	329.5 (57.7) 3.6%	333.3 (45.9) 4.7%	312.5 (60.1) 4.2%	296.3 (45.2) 5.2%
	Invalid	338.8 (58.5) 2.6%	311.3 (46.7) 2.6%	311.0 (45.5) 6.3%	317.9 (51.0) 3.1%	289.0 (52.7) 2.6%	299.3 (47.4) 0.5%
SPL	Valid	360.1 (86.9) 4.7%	329.4 (88.3) 3.1%	330.0 (87.0) 2.6%	333.6 (83.8) 5.2%	314.1 (80.7) 3.1%	311.1 (73.1) 2.1%
	Invalid	334.4 (64.0) 3.6%	304.5 (61.8) 2.1%	314.8 (60.1) 3.1%	323.0 (80.6) 5.2%	305.4 (73.9) 7.8%	303.0 (66.0) 1.6%

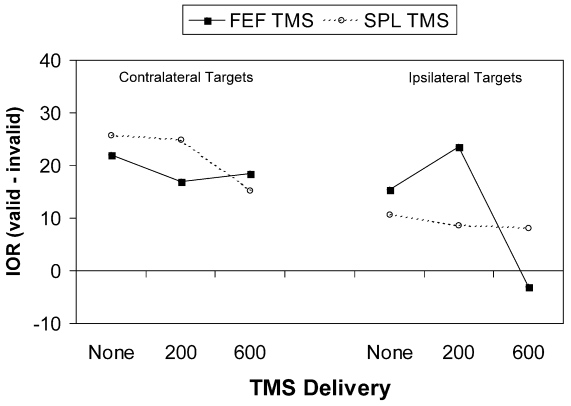

Fig. 2 The magnitude of inhibition of return (IOR), derived by subtracting the invalid reaction time (RT) from the valid RT, is shown separately for each visual hemifield and transcranial magnetic stimulation (*TMS*) site, as a function of the TMS delivery condition. The FEF stimulation conditions are represented by *solid lines* and *black filled squares*, whereas the superior parietal lobule (*SPL*) stimulation conditions are represented by *dashed lines* and *unfilled circles*. *Positive values* indicate that the valid RT was slower than the invalid RT, and thus the presence of IOR, whereas negative values indicate the absence of IOR or a facilitatory effect. Note the complete loss of IOR in the FEF stimulation condition only at the 600 ms stimulus onset asynchrony (SOA) when the cue and target appear in the hemifield ipsilateral to the TMS

to biasing attention and eye movements in contralateral directions, is also involved with contralateral visual processing and target selection.

These results were confirmed with two separate three-way ANOVAs, one for each TMS site, with cue validity (valid vs. invalid), target side (ipsilateral vs. contralateral to the TMS), and TMS delivery (no TMS vs. 200 ms vs. 600 ms) as the three within-subject factors. For the three-way ANOVA on the FEF data, there was a significant main effect of cue validity, reflecting IOR due to slower responses to targets appearing at previously cued locations [$F(1, 7)=6.927$, $P<0.05$]. In addition, there was also a significant main effect of target side due to delayed responses to targets appearing in the visual hemifield contralateral to the TMS [$F(1,7)=13.510$, $P<0.01$]. The main effect of TMS delivery was also significant; responses were slower when no TMS pulse was delivered [$F(2,14)=14.964$, $P<0.001$] demonstrating a general alerting effect of the TMS pulse, probably due to the sound artifact, on RT that is independent of spatial attention (Posner and Boies 1971). Most importantly, there was a significant three-way interaction between cue validity, target side, and TMS [$F(2,14)=6.177$, $P<0.02$]. This interaction was due to the complete absence of IOR for ipsilateral targets in the 600 ms TMS condition. None of the other interactions in the frontal eye field TMS condition approached significance (all $Ps>0.10$).

For the SPL control conditions, a significant effect of cue validity was measured [$F(1,7)=4.499$, $P<0.05$ with a directional test since IOR was expected], indicating the presence of IOR. A significant main effect of TMS delivery was also measured [$F(2,14)=13.779$, $P<0.001$]. The RT patterns contributing to these two main effects were identical to the respective main effects in the FEF condition. There was also a marginally significant target side×TMS delivery interaction [$F(2,14)=2.89$, $P<0.09$], due to a smaller difference between left and right target detection when the TMS pulse occurred 200 ms after cue onset. Most importantly, and in contrast to the FEF condition, the main effect of target side and all of the remaining interactions did not approach significance [all $Ps>0.10$].

Although the validity×target side interaction for the SPL condition was not statistically significant ($P>0.15$), the magnitude of IOR for targets on the side ipsilateral to the SPL TMS was overall smaller than the IOR observed for targets on the contralateral side (see Fig. 2). This prevented the interaction, as measured in separate ANOVAs, of the magnitude of IOR for ipsilateral targets in the FEF vs. SPL conditions at the 600 ms SOA to achieve significance [$P>0.20$ for the TMS site×validity interaction at this SOA] and produced a trend for more IOR for targets ipsilateral to the FEF stimulation as compared to SPL stimulation at the 200 ms TMS SOA, as reflected by the TMS site×validity interaction at the 200 ms SOA [$F(1,7)=4.033$, $P=0.085$]. Because the SPL was localized only anatomically with respect to the motor cortex, unlike the FEF that was also functionally localized, variability across subjects was likely in terms of the SPL site stimulated. However, since this site only served

as a control site, and clearly did not demonstrate the same modulations of IOR as with TMS of the FEF, its purpose as a control TMS site was achieved. Thus, the loss of IOR with TMS of the FEF must be due to the specific location and timing of the TMS pulse over this cortical region rather than some general, non-specific cortical effect.

Discussion

Although the superior colliculus has been suggested to be directly involved with generating IOR (Posner et al. 1985; Sapir et al. 1999), as well as in the initial orienting and movement of attention to the cued location (Rafal et al. 1988), our results show, to the contrary, that the FEF is the critical brain region necessary for producing this attentional bias away from previously cued locations. When single-pulse TMS was applied only over the right FEF 600 ms after the cue and 150 ms before the target, IOR was no longer measured in the ipsilateral hemifield. This result is consistent with a recent study suggesting that the superior colliculus codes IOR, but that it is generated within some cortical site (Dorris et al. 1998; Dorris et al. 2002). Thus, activation within the superior colliculus is necessary but not sufficient for generating IOR since without it no initial orienting of attention will take place (Rafal et al. 1988), thereby negating the necessity for a bias against reorienting attention to that same location.

We also showed that TMS of the FEF, but, importantly, not the SPL, delays responses to visual targets in the contralateral hemifield suggesting that the human FEF, like in monkeys (Schall and Thompson 1999), is also involved with visual target selection. Because this visual field difference was also apparent in the randomly interleaved no TMS trials in the FEF stimulation block, but not in the SPL stimulation block, there may have been tonic disruption of the visual selection cells in the FEF due to TMS, but not the oculomotor cells involved with the generation of inhibition of return. Note that all of our subjects initially received approximately 10 min 0.3 Hz FEF stimulation due to the anatomical localization procedure (Ro et al. 1999; Ro et al. 2002), and that this along with the intermittent TMS pulses delivered to the FEF in this condition may have produced disruption of visual processing beyond the immediate effects of the TMS pulse, as has been shown with 1 Hz stimulation (Chen et al. 1997; Kosslyn et al. 1999). Although no lasting effects of 0.3 Hz TMS have been reported, there may nonetheless be some modulations as a result of it. Future work is necessary to determine whether this is so.

Since TMS of the FEF eliminated only ipsilateral IOR and delayed contralateral visual processing, the mechanism that is likely to be operating is an FEF inhibition of reflexive glances to the ipsilateral cue by the programming of a voluntary saccade in the opposite direction (see Fig. 3). This counter-vector saccade program, which serves to help inhibit or cancel reflexive saccadic eye movements in the opposite direction, thus leads to the generation of IOR and enhanced contralateral visual processing. This is consistent with claims from psychophysical studies suggesting that IOR arises from the necessity to inhibit reflexive glances to cues (Chelazzi et al. 1995). This proposed mechanism is also consistent with our previous results demonstrating that the FEFs are primarily involved with the programming of voluntary, but not reflexive saccades (Henik et al. 1994; Ro et al. 1997; Ro et al. 1999) and with the inhibition of reflexive glances (Rafal et al. 2000). Furthermore, this explanation can also account for the recent demonstrations of cross-modal IOR between all possible pairings of visual, somatosensory, and auditory stimuli (Spence et al. 2000). Since the colliculus is involved with generating reflexive glances to stimuli from different sensory modalities (Groh and Sparks 1996), the FEF must also counteract this natural tendency to saccade to the location of the sensory stimulus resulting in IOR.

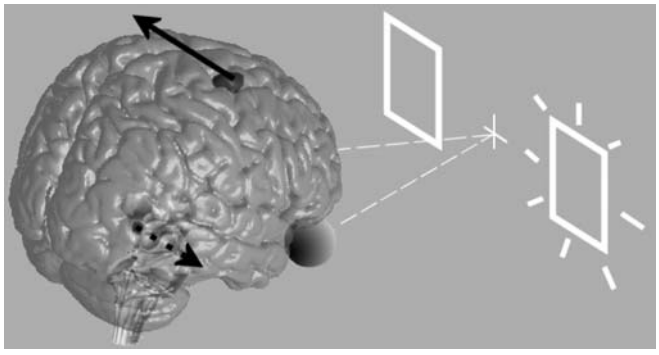

Fig. 3 A schematic of the proposed neural mechanism underlying IOR. When a visual cue is presented, the superior colliculus (SC) reflexly orients towards the cue and generates a motor command for a saccade towards it (*dotted arrow*). However, the opposite FEF generates an opposing saccade command to help maintain the required fixation, leading to the reorienting of attention towards the novel hemifield (*solid arrow*). This latter command generated in the FEF leads to the genesis of IOR resulting in enhanced visual detection on the side contralateral to the cue. When the FEF ipsilateral to a cue is stimulated with appropriately timed TMS, IOR cannot be generated

Since no neutral cues were used in this experiment, we cannot determine whether the amelioration of IOR ipsilateral to the FEF stimulation was due to a speeding up of responses to validly cued targets or delaying of responses to invalidly cued targets. However, inspection of the data in Table 1 for the ipsilateral targets in comparison to the contralateral targets in the FEF conditions suggests that both may have been the case. Although the selection of an appropriate neutral cue can be problematic (Jonides and Mack 1984), future studies employing a neutral cue of some sort might be informative at revealing the exact nature of this effect. Regardless of how the IOR effect is abolished, our results suggest the normal IOR effects, as measured by slower RTs to validly cued targets in comparison to invalidly cued targets, are no longer present following stimulation of the FEF shortly before the target.

One may question why no effects on IOR were observed with TMS over the FEF at the 200 ms SOA. Although IOR is typically more robust and present after approximately 250 ms (Posner and Cohen 1984), IOR has also been detected at SOAs less than 200 ms (e.g. see Tassinari et al. 1994). There are two main reasons why TMS probably did not influence IOR when the pulse was delivered shortly after the cue. First, at these short intervals after a cue, as at the 200 ms SOA used in this experiment, there typically is early facilitation that counteracts IOR (Maruff et al. 1999; Collie et al. 2000). Furthermore, and more importantly, the TMS we used was a single pulse rather than a repetitive train of pulses. Therefore, when we stimulated 200 ms after the cue, in addition to facilitation counteracting IOR, there was also time for the FEF to recover from the effects of TMS to induce IOR by the later interval at which the target appeared. Regardless of the exact reason why no effects of FEF TMS on IOR at the 200 ms SOA were observed, the results suggest that IOR may only be disrupted from FEF TMS if the TMS is applied close to the time of the target.

Our results also serve to clarify findings from a recent fMRI study demonstrating right FEF activation with IOR (Lepsien and Pollmann 2002). In that study, right FEF activation was measured with IOR, but the mechanisms and laterality effects underlying this activation were unclear. The TMS results reported in the current study reveal that the nature of this right FEF activation in the generation of IOR was likely due to oculomotor programming away from the right cued location at longer cue-to-target SOAs. Further work will need to address the lack of left FEF activation in their study and whether TMS of the left FEF will produce similar alterations in IOR generation.

Although previous studies have demonstrated effects of TMS on remote neural structures (Fox et al. 1997; Paus et al. 1997), it is unlikely that the FEF stimulation in our study produced functional modulations in the superior colliculus and/or the parietal lobe that biased our results. Previous studies have shown that TMS of the frontal eye fields, functionally located as in the present study, does not modulate exogenously driven, reflexive saccades (Ro et al. 1997), suggesting the influences of TMS on the superior colliculus to be minimal. Other studies have failed to demonstrate that lesions of the parietal cortex modulate IOR (Posner et al. 1985). Also note that our control site involved a region of the parietal cortex and no modulations were observed in this condition. Therefore, our results are most likely to be due to a direct FEF interference of the processes leading to inhibition of return. TMS over the parietal eye fields or parietal reach regions (Andersen et al. 1997), however, may be informative regarding the possible contributions of the parietal cortex to IOR.

These results demonstrate that attention and eye movements are tightly coupled and that the same neural structures in humans give rise to both of these behaviors (Rizzolatti et al. 1987; Kustov and Robinson 1996; Corbetta et al. 1998; Nobre et al. 2000; Moore and Fallah 2001). They show that IOR is generated within the FEF rather than being generated within the superior colliculus as previously conceived (Rafal et al. 1988; Dorris et al. 1998; Sapir et al. 1999; Dorris et al. 2002). In conjunction with the finding in our study demonstrating contributions to visual selection from the FEF, we propose that IOR is the behavioral byproduct of a mechanism that operates by biasing attention away from previously cued locations through programming of contralateral voluntary eye movements in the FEF ipsilateral to the cue. This FEF activation then also serves to enhance visual processing in contralateral locations (c.f. Grosbras and Paus 2002).

Acknowledgements We thank Bob Rafal and Ayelet Sapir for helpful comments on earlier drafts of this manuscript and John Ashburner for assistance with SPM99 and Matlab. This research was supported by the US PHS and the Human Frontiers Science Program.

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