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Modulation of Antisaccades by Transcranial Magnetic Stimulation of the Human Frontal Eye Field

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It has been suggested that the frontal eye field (FEF), which is involved with the inhibition and generation of saccades, is engaged to a different degree in pro- and antisaccades. Pro- and antisaccades are often assessed in separate experimental blocks. In such cases, saccade inhibition is required for antisaccades but not for prosaccades. To more directly assess the role of the FEF in saccade inhibition and generation, a new paradigm was used in which inhibition was necessary on pro- and antisaccade trials. Participants looked in the direction indicated by a target ('<' or '>') that appeared in the left or right visual field. When the pointing direction and the location were congruent, prosaccades were executed; otherwise antisaccades were required. Saccadic latencies were measured in blocks without and with single pulse transcranial magnetic stimulation (TMS) to the right FEF or a right posterior control site. Results showed that antisaccades generated into the hemifield ipsilateral to the TMS were significantly delayed after TMS over the FEF, but not the posterior control site. This result is interpreted in terms of a modulation of saccade inhibition to the contralateral visual field due to disruption of processing in the FEF.

Keywords: eye movements, inhibition, reflexive saccades, TMS, voluntary saccades

Introduction

Eye movements allow a fast and efficient exploration of the visual world. Typically, salient stimuli trigger eye movements towards them to bring the region of interest into the fovea, the retinal area of highest spatial resolution. In addition to such reflexive saccades, effective exploration requires voluntary control, such as the inhibition of reflexive saccades and the generation of saccades in another direction. In such a situation the reflexive and the voluntary systems for visual orienting are in direct competition.

In the laboratory the competition between the reflexive and the voluntary system can be investigated by testing inhibition and execution of reflexive and voluntary saccades using the pro- and antisaccade task. In a typical prosaccade task the participant fixates a central stimulus and then makes a saccade to a peripheral stimulus that abruptly appears. In the antisaccade task the display remains the same as in the prosaccade task but now the participant is supposed to inhibit the reflexive saccade toward the stimulus and to saccade in the opposite direction. Clearly, performance of such pro- and antisaccades requires different processes. Prosaccades are reflexive responses triggered by the onset of a stimulus. Antisaccades require at least two processes: the inhibition of a prosaccade and the volitional programming of a saccade in the opposite direction. Additionally, it has been suggested that a shift of attention from the stimulus location to the endpoint of the antisaccade has to take place on antisaccade trials (Olk and Kingstone, 2003).

Considering the different processes involved in pro- and antisaccades, one can expect that distinct brain areas mediate these different kinds of saccadic eye movements. Neurophysiological and neuropsychological studies have revealed the role of the superior colliculus (SC) and the parietal lobe in the generation of reflexive prosaccades (Pierrot-Deseilligny *et al.*, 1991; Everling *et al.*, 1998; Gaymard *et al.*, 1998). For the inhibition of reflexive saccades and the generation of voluntary antisaccades, structures in the frontal lobe such as the frontal eye fields (FEF) and supplementary eye fields (SEF) have been implicated (Guitton *et al.*, 1985; Henik *et al.*, 1994; Ro *et al.*, 1997; Schlag-Rey *et al.*, 1997; Rafal *et al.*, 2000). Pierrot-Deseilligny *et al.* (1991) reported an increased rate of saccade direction errors bilaterally in the antisaccade task following dorsolateral prefrontal cortex (dlPFC) lesions, consistent with a role of this area in saccade inhibition, short-term spatial memory, decisional processes and maintaining instruction set (Pierrot-Deseilligny *et al.*, 1991, 2004). These cortically generated eye movement signals can be conveyed directly or indirectly via the basal ganglia and substantia nigra to the SC and also directly to the brain stem saccade generators (for reviews, see Schiller, 1984; Everling and Fischer, 1998).

The present paper is concerned with the role of the FEF in saccade generation and inhibition in the pro- and antisaccade tasks. Imaging studies (O'Driscoll *et al.*, 1995; Connolly *et al.*, 2000; DeSouza *et al.*, 2003) have shown a significantly greater increase of cerebral blood flow in the FEF for antisaccades than prosaccades, suggesting that the FEF might be more involved in antisaccades than in prosaccades. Such higher activation could reflect the role of the FEF in voluntary saccade generation. Converging evidence shows FEF involvement particularly in the triggering of voluntary saccades. Chronic unilateral lesions of the FEF and disruption of the FEF with transcranial magnetic stimulation (TMS) leads to increased latencies for voluntary contralesional saccades (Henik *et al.*, 1994; Ro *et al.*, 1997, 1999). Gaymard *et al.* (1999), who observed prolonged antisaccades bilaterally in a patient with a FEF lesion, suggest that triggering antisaccades in the correct direction (i.e. saccades to an internally represented target) involves the FEF.

On the other hand, higher activation could also mirror involvement in saccade inhibition (Hunt *et al.*, 2004). Correct performance on antisaccade trials seems to be at least partly dependent on FEF top-down control, as similar discharge patterns between FEF and SC neurons have been reported (Everling and Munoz, 2000). The relationship between activation patterns in the FEF and SC, which can be used to predict whether a reflexive saccade will occur, cannot necessarily be interpreted

in terms of the inhibition signal originating in the FEF. However, a study by Burman and Bruce (1997) tested suppressive effects of electrical stimulation of the FEF in pro- and antisaccades, and concluded that FEF suppression sites could be involved in the competition with and suppression of signals that might direct the eyes toward a salient feature. Electrical stimulation applied to 'pure suppression sites' of the FEF led, for example, to delayed contraversive visually guided saccades. Prosaccades were completely suppressed during FEF stimulation and saccade initiation was delayed until poststimulation.

Neuropsychological support for a role of the FEF in saccade inhibition is equivocal (Machado and Rafal, 2004; but see Gaymard *et al.*, 1999). A concern with the interpretation of neuropsychological studies is, however, that results may be affected by brain reorganization and compensatory mechanisms in patients with chronic lesions and effects of diaschesis, such as hypoactivity of the ipsilesional colliculus (Henik *et al.*, 1994), after acute FEF lesions. Based on the inconsistencies between these patient studies, perhaps due to these 'side effects' of naturally occurring lesions, the role of the FEF in saccade inhibition might further be elucidated by transiently and reversibly disrupting the FEF with transcranial magnetic stimulation (TMS). TMS provides a unique means to study the contribution of stimulated cortical areas in oculomotor control (Merabet *et al.*, 2003) because the stimulation allows temporary modulation of processing in cortical brain areas such as the FEF. Thus, reorganization and effects of diaschesis are not of concern with 'virtual' brain lesions induced by TMS.

In one study using TMS to investigate oculomotor function, Müri *et al.* (1991) applied TMS to the FEF during a visually guided prosaccade task at 60–100 ms after stimulus onset. No effects on saccade latency were found. In an antisaccade task Müri *et al.* (1991) applied TMS to the FEF between 50–110 ms after target onset. Latencies of rightward antisaccades increased when TMS was triggered over the right FEF 50–100 ms after stimulus onset. In female subjects leftward antisaccades were also prolonged. No effects emerged when TMS was applied over the median nerve, right facial nerve or 3 cm posterior to the vertex on the parietal cortex in the antisaccade task. According to the authors, this delay could indicate that antisaccades are compromised in the contralateral visual field of the stimulated FEF, suggesting either reduced attention in the contralateral visual field or insufficient suppression of reflexive saccades. No increase in the percentage of erroneous saccades to the target was observed, however.

In a further TMS study, by Terao *et al.* (1998), effects on latencies of antisaccades but not prosaccades emerged, consistent with the study by Müri *et al.* (1991). Compared with a baseline without TMS, antisaccade latencies were delayed when TMS was applied at 80 ms after target presentation over posterior parietal regions (6–8 cm posterior/0–4 cm lateral to the hand area) and at 100 ms over frontal areas (2–4 cm anterior and 2–4 cm lateral to the hand area). The effects were independent of stimulated hemisphere or antisaccade direction. Importantly, in this study the number of erroneous saccades to the stimulus increased with TMS over the contralateral hemisphere in antisaccade trials, indicating compromised saccade inhibition.

Both TMS studies show that 'lesioning' the FEF results in prolonged antisaccade latencies, but only Terao *et al.* (1998) show that saccade direction errors increased. While it is not clear from the methodology described in the paper by Müri *et al.* (1991) whether leftward and rightward saccades were interleaved or assessed in separate blocks, the authors state that targets appeared at a predictive position at random time intervals. It is possible that no effect on saccade direction errors was observed because targets were presented at predictive positions. Knowledge of the required saccade direction allows participants to prepare saccade direction before target onset, possibly leading to a reduction of error rates. Additionally, a comparison of effects on pro- and antisaccades was hindered by a between-subjects design in the study by Müri *et al.* (1991). A further limitation that pertains to both studies is the localization of FEF. In the study by Müri *et al.* (1991) TMS was applied over the presumed right FEF (2 cm in front of earline, 5 cm lateral to sagittal midline). In the Terao *et al.* (1998) study, rather large areas were defined as effective in influencing saccadic latencies. The frontal area very likely included the FEF but probably also other oculomotor and memory areas, such as the dorsolateral prefrontal cortex.

In the present study we sought to investigate the role of the FEF in the generation and inhibition of pro- and antisaccades using TMS, while defining the FEF more precisely and functionally (Ro *et al.*, 1999, 2002). The present study differed in another important aspect from the two previous TMS studies. Müri *et al.* (1991) and Terao *et al.* (1998) assessed pro- and antisaccades in separate blocks. In such a paradigm inhibition is only required for antisaccades, not prosaccades. We therefore used a paradigm in which pro- and antisaccades are randomized and both types of saccades require oculomotor inhibition (Olk and Kingstone, 2003). The instruction of whether a pro- or an antisaccade has to be generated is given by the target stimulus. At the beginning of each trial participants fixate the centre of the display, not knowing what type of saccade will be required. The target, a left- or right-pointing arrowhead, then appears in the left or right visual field. Participants are required to decode in which direction the target points while maintaining fixation and then saccade in the direction indicated by the arrowhead. This paradigm instructs prosaccades when arrowhead direction and visual field are congruent (e.g. '<' in the left visual field), and antisaccades when they are incongruent (e.g. '<' in the right visual field). Note that we use the term 'prosaccade' not for a purely reflexive saccade, but for a saccade that is generated to the position of a visual stimulus. A crucial feature of this paradigm is that oculomotor inhibition prior to target presentation is matched across pro- and antisaccades because arrowhead direction has to be discriminated before a saccade is executed. Further, saccade inhibition is now also required for prosaccades, contrary to a blocked paradigm. This not only makes effects between saccades more comparable, but also allows to investigate the role of the FEF in saccade inhibition on prosaccade trials.

Materials and Methods

Participants

Eleven subjects gave informed consent and reported having normal or corrected vision and no history of any neurological disorders. Subjects were paid for their participation. The research was approved by the local Institutional Review Board of Rice University. All candidates were screened with the FEF localizer task (described below). Five participants (mean age = 27.4 years, two male, three female) met the criteria of no saccade latency asymmetry without TMS and longer saccadic latencies for leftward saccades following frontal TMS stimulation in the localizer task and completed the entire study. Candidates for whom a saccadic

reaction time asymmetry was found in the baseline condition or saccadic latencies were not affected by the TMS were excluded.

Stimuli and Procedure

Eye position was monitored at a rate of 1000 Hz using an Eye-Trac 210 eye tracker (ASL, Bedford, MA). Saccade latencies were defined by a velocity criterion (velocity of saccade > 50°/s). Each block was preceded by a three-point calibration. TMS was performed using a MES-10 polyphasic stimulator (Cadwell Laboratories, Kennewick, WA; 2.2 T magnetic field at maximum intensity) and a focal, figure-eight coil (each component measuring 4.5 cm in diameter). A PC was used for triggering the MES-10, stimulus presentation and recording eye position. Stimuli were shown on a Sony Trinitron Multiscan monitor. The timing of visual displays was controlled by the vertical synchronization of the computer monitor at 16.7 ms intervals (60 Hz).

The hand area of the right motor cortex was first localized. The most anterior area of the motor cortex that produced the most reliable, visible contraction of the contralateral left hand was determined and marked on the scalp using a grease pencil. TMS intensity was adjusted until a contraction of the hand was barely visible. This intensity setting was defined as the hand area motor threshold. To localize the FEF, the subjects performed a saccade task. A fixation cross (0.1° in diameter) was presented centrally along with two unfilled squares (1°) at 10° to the left and right. After 2000 ms, an arrowhead (height: 1°, width: 0.5°) appeared in the centre. Arrowhead direction was randomized, pointing to the left or right for 25 trials each. Stimuli were white on black background. Subjects were seated 57 cm from the monitor and maintained fixation until arrowhead onset and then looked as quickly and accurately as possible at the lateral box towards which the arrowhead was pointing. Following the saccade, subjects' eyes returned to centre. In the first block (no TMS) baseline saccade latency was measured. After discarding trials with saccade direction errors, mean latencies of left- and rightward saccades were compared (*t*-test). If no difference between left and right saccades was obtained, the TMS coil was positioned at a site at least 1 cm anterior to the hand area varying coil position in steps of 0.5 cm in the sagittal or coronal plane in different blocks until a site was found that produced saccadic latency asymmetries with longer left- than rightward saccades from TMS. This site was defined as the FEF (Table 1). The TMS pulse (10% above motor threshold) was administered during this functional localization procedure on each trial 50 ms before arrowhead onset. The axis of the coil was angled at 90° from the mid-sagittal axis. We applied such strict criteria for localizing the FEF as it has been shown that the FEF is mainly involved in controlling contralateral saccades (Ro *et al.*, 1997, 1999). For a more detailed description of this procedure, see Ro *et al.* (2002).

In the experimental task a central fixation cross (0.5°) was shown without lateral placeholders. After 2 s an arrowhead (0.5°) was presented at 7° to the left or right of fixation. Participants were to look in the direction indicated by the arrowhead and had a time window of 1 s to do so. Pro- and antisaccades were randomized. A prosaccade occurred when arrowhead direction and visual field (VF) were congruent (e.g. '<' in LVF), and an antisaccade occurred when they were incongruent (e.g. '<' in RVF). Note that because arrowhead direction had to be discriminated before a saccade was executed, oculomotor inhibition prior to target presentation was matched across pro- and antisaccades. Each of five blocks consisted of 100 trials, 50 for each saccade type. The direction and location of the arrowhead were randomized, leading to 25 trials of leftward and 25 trials of rightward prosaccades, as well as 25 trials requiring leftward and 25 trials requiring rightward antisaccades. Instructions emphasized speeded but accurate responding. In the first block (no TMS) baseline latencies were measured. In the following four blocks location and timing of TMS were counterbalanced. TMS was applied over the right FEF and a right control site. The control site was located in a homologous posterior location to the FEF stimulation site with respect to the motor hand area. This was either 1.5 or 2 cm posterior of the motor hand area (see Table 1 for details). The control area was thus not located in a known eye-movement area such as the human analogue for LIP, which is located more posterior and ventrally. Effects of TMS on saccadic reaction time and saccade errors were therefore expected to occur only in the FEF stimulation condition. FEF and control site stimulation was given for two blocks each and TMS was administered on every trial during all four blocks, resulting in 400 TMS pulses for each participant. Block order was randomized. TMS was applied at an early (50 or 100 ms) and at a late (100 or 150 ms) stimulus onset asynchrony (SOA) after arrowhead onset. SOAs were selected based on a participant's saccade latency in the baseline condition. In a pilot experiment with six subjects TMS had been applied, as in the FEF localizer task, 50 ms before arrowhead onset. Although this SOA yielded effects in the simpler localizer task, the timing did not prove efficient in the more complex experimental task, in which saccade latencies tended to be about 100–150 ms longer. In the present study we therefore adjusted SOA depending on baseline latencies for each subject.

Data were analyzed based on planned comparisons using ANOVAs with repeated measures as well as *t*-tests. Only saccades with an amplitude of more than 0.4° and latencies within 2.5 SD of the mean of that condition were included. Trials in which the first saccade was made in the incorrect direction were classified as saccade direction errors and were analyzed separately.

Results

Saccadic Latencies

The group results are illustrated in Figure 1. Individual data is presented additionally in Figure 2. A saccade type (prosaccade/antisaccade) × saccade direction (left/right) repeated measures ANOVA on the mean latency of saccades in the no TMS condition showed no significant effects.

The impact of stimulation over FEF and the control site was tested with separate repeated measures ANOVAs for each TMS

Table 1

TMS motor threshold, location of FEF and control site with respect to the hand area of the motor cortex, saccadic latencies of leftward and rightward saccades with FEF stimulation in the localizer task and scalp measurements for each subject

Subject	TMS motor threshold	FEF location (cm)		Control site location (cm)		Saccadic latency (ms)		Scalp measurements (cm)			
		x	*y*	*x*	*y*	Leftward	Rightward	MN	MI	LM	RM
1	60	2	−0.5	−2	−0.5	239.78	215.93	14.5	18	15.5	13.5
2	63	2	0	−2	0	230.63	213.44	16.5	18	18.5	12
3	49	1.5	0.5	−1.5	0.5	211.19	190.58	16	19	18.5	12.5
4	53	2	0	−2	0	274.25	247.5	17	19	19	14
5	56	1.5	1	−1.5	1	245.0	231.0	16.5	15	19	12

The *x*-values indicate the location of FEF and the posterior control site (in cm) varying along the sagittal plane, with positive values rostral and negative values caudal, and the *y*-values indicate positions (in cm) varying along the coronal plane, with positive values dorsal and negative values ventral. *x* and *y* are defined relative to the hand area. Columns 7 and 8 list saccadic latencies of leftward and rightward saccades in the localizer task with TMS over the designated FEF. Columns 9–12 give distances measured along the scalp: MN, distance from right motor hand area to nasion; MI, distance from inion to right motor hand area; LM, distance from left ear to right motor hand area; RM, distances from right ear to right motor hand area.

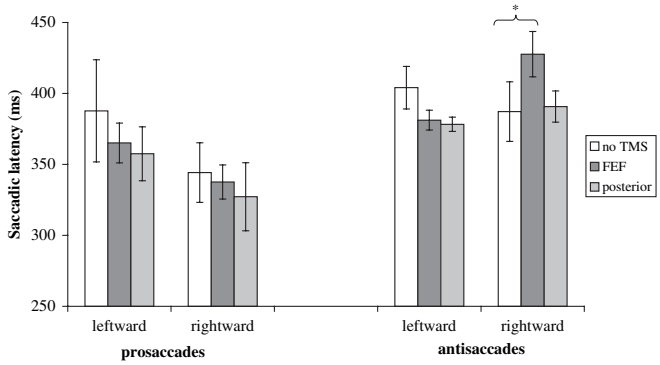

Figure 1. Mean saccadic latencies (in ms) for prosaccades and antisaccades, separately for stimulation condition and direction of eye movement. Data were averaged across SOA as effects of SOA were not significant for FEF stimulation. Error bars represent normalized standard errors. The asterisk highlights the significantly longer rightward antisaccades with FEF stimulation compared with baseline.

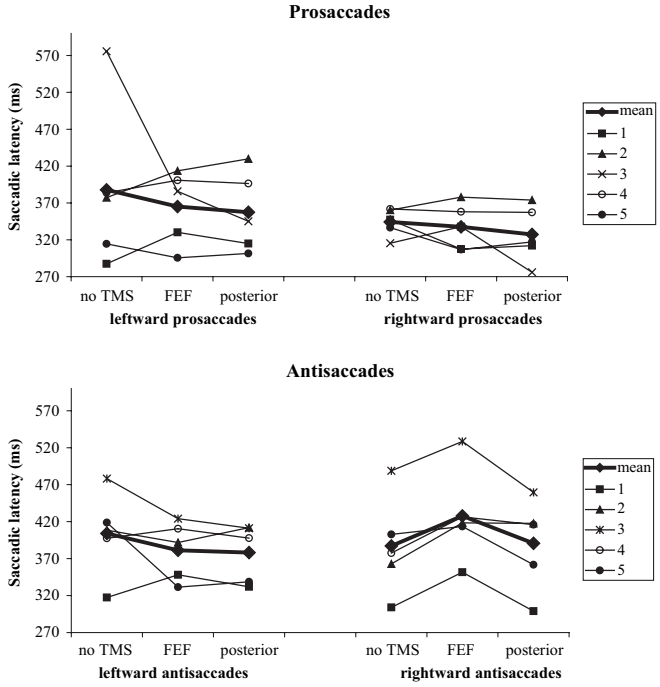

Figure 2. Mean saccadic latencies (in ms) for prosaccades and antisaccades, plotted separately for each stimulation site and for direction of saccade. The data averaged across SOA are shown for the group of subjects (thick line) and each individual subject (thin lines).

site. The factors in each analysis were saccade type (prosaccade/antisaccade), saccade direction (leftward/rightward) and SOA (short/long). The analysis for the FEF stimulation data showed a significant main effect of saccade type [$F(1,4) = 8.4$, $P = 0.044$], indicating longer latencies for antisaccades than prosaccades. Further, an interaction between saccade type × saccade direction [$F(1,4) = 12.4$, $P = 0.024$] pointed to a pattern of longer latencies of leftward than rightward prosaccades (365 versus 338 ms) but longer rightward than leftward antisaccades (428 versus 381 ms, respectively). The latency differences between leftward and rightward prosaccades and between leftward and rightward antisaccades were not significant as tested with *t*-tests.

To evaluate the effects of FEF stimulation in relation to baseline, *t*-tests compared latencies of leftward and rightward pro- and antisaccades made in the baseline condition and with FEF stimulation (averaged over SOA, as this factor is not present for the no TMS condition). Latencies for rightward antisaccades with FEF stimulation were significantly longer than in the no TMS baseline condition [baseline: 387 ms, FEF stimulation: 428 ms; $t(4) = 5.16$; $P = 0.007$]. The remaining three comparisons between leftward prosaccades, rightward prosaccades and leftward antisaccades with FEF stimulation and baseline were not significant.

Stimulation over the posterior control site showed no significant effects apart from a main effect of SOA [$F(1,4) = 8.5$, $P = 0.044$]. Latencies were faster for short SOAs. This effect might be due to intersensory facilitation of the TMS associated click on the processing of the visual target or from subjects waiting until after the TMS pulse to respond (Sawaki *et al.*, 1999). The lack of a SOA effect for the FEF condition may be due to the TMS also disrupting the saccades at certain SOAs. TMS influences on the FEF, and as a result on saccade initiation, may have counteracted the effects of intersensory facilitation and the tendency for subjects to wait for the TMS pulse. Importantly, *t*-tests comparing the latencies of leftward and rightward pro- and antisaccades between the posterior TMS versus the no TMS baseline yielded no significant results. No effect of saccade type was observed. Numerically antisaccades had longer latencies than prosaccades.

Saccade Direction Errors

As for saccade direction errors, no significant effects were obtained for the no TMS data (ANOVA with the factors saccade type and saccade direction) and for the FEF stimulation data (factors saccade type, saccade direction, SOA). Stimulation over the control site resulted in a significant interaction between saccade type × saccade direction [$F(1,4) = 40.8$; $P = 0.003$]. More errors occurred on trials requiring a rightward than a leftward antisaccade (11.1 versus 7.8%, respectively); for prosaccades this pattern was reversed with more errors for leftward than rightward prosaccades (4.5 versus 3.4%, respectively). The baseline data, however, showed the same pattern and no significant effects emerged when comparing baseline and posterior stimulation (*t*-tests). Error rates are given in Table 2.

Discussion

Previous work using fMRI suggests that the FEF might be more involved in antisaccades than prosaccades (O'Driscoll *et al.*, 1995; Connolly *et al.*, 2000; DeSouza *et al.*, 2003). It is unclear, however, which function of the FEF such increased activation may reflect. A greater involvement of the FEF for antisaccades could reveal its role in the generation of voluntary saccades and in the suppression of reflexive saccades, or both. The present study investigated the role of the FEF in pro- and antisaccades using TMS. In contrast to previous TMS studies applying the pro- and antisaccade task, the FEF was localized functionally and more precisely. Additionally and contrary to prior studies where suppression of a saccade to the target was required only on antisaccade trials because pro- and antisaccades were assessed in separate blocks, in the present study inhibition prior to saccade execution was required for pro- and antisaccades. Because inhibition was employed also on prosaccade trials, the overall differences in saccadic latencies between pro- and

Table 2
Mean error rates (in %) for all conditions

	Prosaccades		Antisaccades	
	Leftward	Rightward	Leftward	Rightward
No TMS	3.3	1.6	18.2	21.9
FEF	3.4	2.6	14.3	19.9
Control site	4.5	3.4	7.8	11.1

antisaccades were small (Olk and Kingstone, 2003), and only reached significance when TMS was applied over the FEF and affected performance.

The main result of the study indicated that TMS over the right FEF increased latencies of rightward antisaccades but had no effect on prosaccades. As TMS was administed at 50, 100 or 150 ms after the visual target onset, and based on the mean saccadic latency across all TMS conditions excluding the condition affected by TMS (i.e. the rightward antisaccade condition with FEF stimulation), the TMS pulse was estimated to be applied on average at 268 ms before saccade onset. On trials requiring a rightward antisaccade, FEF stimulation was on average applied at 333 ms before antisaccade onset. Because the latter value contains the significant TMS effects on rightward antisaccades, the difference of 65 ms provides an estimate of the TMS effect on rightward antisaccades with FEF stimulation (see also Fig. 1). Which processes likely took place at ~333 ms before saccade onset on trials of rightward antisaccades and could have been disrupted? Possible accounts for this finding and the underlying mechanisms will be presented and evaluated in turn.

A candidate explanation of the results could originate in the FEF's role not only in eye movements, but also for the allocation of attention (Corbetta *et al.*, 1998; Ro *et al.*, 2003; Moore and Fallah, 2004). In the present task, attention had to be directed to the stimulus for discrimination. In prosaccade trials attention could remain at that location as the saccade was directed to the stimulus. For antisaccades, attention had to be disengaged from the stimulus and moved to the opposite hemifield, into which the antisaccade had to be made. Recently, Grosbras and Paus (2002) suggested that TMS over the FEF could enhance the engagement of attention. If TMS over the right FEF enhanced attention to the LVF (location of the arrowhead for rightward antisaccades), it could be that disengagement from the stimulus was hampered, leading to an increase in the time needed to disengage from the stimulus in the LVF and to move attention to the RVF, the location to which the antisaccade had to be made. This could result in increased latencies for rightward antisaccades. This explanation is unlikely, however, as Grosbras and Paus (2002) found that TMS over the right FEF enhanced attention to both VFs and not selectively to the LVF. Additionally, the reported effects occurred when TMS was applied 53 ms before target onset. In our study TMS was always applied after target onset. In addition, enhancement of attention to the LVF should have resulted in faster leftward prosaccades with FEF stimulation compared with baseline as the stimulus is presented in the LVF. This was not the case. Additionally, the effects of single-pulse TMS are usually analogous to 'lesioning' a brain area, and such lesioning of the right FEF should have impaired the allocation of attention to the LVF and thereby processing of stimuli in the LVF according to this attentional account. If such were the case, impaired processing of LVF stimuli should have also occurred for leftward prosaccades as stimulus presentation was in the LVF under these conditions. This also was not observed. It therefore seems that effects on the allocation of attention do not seem to reflect the pattern of results that we obtained.

Even though the allocation of attention might not be affected, the TMS pulse at 50–150 ms after stimulus onset might fall into a time window during which disengagement of attention from the arrowhead in the LVF and moving attention to the RVF might be in progress. Neuropsychological data show a disengage deficit after left and right hemisphere lesions, but more pronounced deficits after right hemisphere lesions (Posner *et al.*, 1984; Losier and Klein, 2001). Patients with right hemisphere lesions show particularly increased response times when redirecting attention from an invalidly cued right visual field to a target appearing in the LVF. In other words, they are impaired at the point of disengaging attention from the ipsilesional visual field. If TMS over the right FEF led to a disengage deficit, leftward antisaccades should have been affected more than rightward antisaccades. Grosbras and Paus (2002) found an effect of TMS over the right FEF on invalid cueing. Reaction times increased for contralateral targets (cue directs attention to the RVF, targets appears in the LVF). However, no effect was found for invalid ipsilateral targets (cue directs attention to the LVF, target appears in RVF), which resembles our condition requiring rightward antisaccades. Our results therefore do not seem to be in agreement with a disengage deficit. However, as we tested the right hemisphere only, which may be more responsible for spatial attention processes, we cannot completely rule out an attentional explanation. An experiment comparing the effects of TMS to the left and right FEF might be informative, even though the disengage deficit has been found in both left and right hemisphere patients (e.g. Posner *et al.*, 1984; Friedrich *et al.*, 1998).

Another alternative is that antisaccade execution might require the inversion or rotation of a saccade direction vector. As the FEF is involved in target and saccade endpoint selection (for further details, see Sato and Schall, 2003) and participates in the transformation of visual signals into saccade motor commands (Schall, 1997; cf. Schall *et al.*, 2002), it might play a role in such an inversion process. TMS could lead to a delay in the inversion or rotation of the vector on antisaccade trials. However, as the FEF's role in vector inversion is currently unknown, this explanation is quite speculative.

A more likely oculomotor account that assumes the impairment of inhibition processes of the FEF provides the most consistent and parsimonious explanation for the results. According to such an account, the FEF is involved in the inhibition of reflexive contralateral saccades, which is a key prerequisite for correct rightward antisaccade execution. If TMS over the right FEF hampers this inhibition process and produces slowed rightward antisaccades without completely disrupting the subject's ability to inhibit a leftward saccade and perform the task (note that no significant effects were found in the FEF condition error data), prolonged rightward antisaccades could result. The programming of the rightward saccade by the left FEF as such might be unimpaired, but its release could be dependent on the efficient inhibition of a leftward eye movement to the stimulus by the right FEF. Our finding thus converges with that of Müri *et al.* (1991), who also reported prolonged rightward antisaccades and concluded that antisaccades might be disordered in the contralateral hemifield of the

affected right FEF and that effects of insufficient suppression of reflexive saccades to the stimulus could account for the longer saccade latencies for rightward antisaccades.

Similar interpretations have been advanced in patients with FEF lesions (Rafal *et al.*, 2000; Machado and Rafal, 2004). Machado and Rafal (2004), for example, showed that patients with chronic, unilateral frontal lesions involving the FEF made more reflexive prosaccade errors towards targets in the contralesional field than the ipsilesional field in an antisaccade task, which was not the case for the frontal patients in whom the FEF was spared. This study shows that FEF inactivation can lead to disinhibition of contralesional saccades (also see Henik *et al.*, 1994; Rafal *et al.*, 2000). Our results, however, extend these findings by demonstrating that the deficit is specifically a result of the FEF influences on oculomotor inhibition of reflexive saccades and, because of the transient nature of TMS, are not a consequence of long-term plasticity and brain reorganization.

Terao *et al.* (1998) showed prolonged antisaccades bilaterally as well as increased contralateral saccade direction errors on antisaccade trials, supporting the inhibition account. There might not have been an effect on saccadic direction errors in the present study because saccade inhibition was required on every trial, including prosaccade trials, until the direction of the saccade was determined. Thus participants would be in a state of general rather than direction-specific inhibition.

It is possible that although the transient effects of TMS on oculomotor function can disrupt processes inhibiting reflexive prosaccades, it does not affect the generation of erroneous prosaccades. Data from patients with very small acute lesions restricted to the FEF also showed increased latencies in the antisaccade task with no increases in antisaccade direction errors (Rivaud *et al.*, 1994; Gaymard *et al.*, 1999). These findings originally led to the conclusion that the FEF does not play a role in saccade inhibition but does in saccade generation, as the latency of correct antisaccades was increased by >300 ms bilaterally. However, it cannot be ruled out, based on these data, that saccades are prolonged precisely because of hampered inhibition processes. Interestingly, Rivaud *et al.* (1994) found in a prosaccade task that the patients' prosaccades were much more prolonged than those of control participants when the central fixation point remained on than when it was removed prior to target onset. While this gap effect (Saslow, 1967) is a common finding, the much enlarged effect for FEF-lesioned patients indicates a role of the FEF in the disengagement of fixation from the central fixation point. Rivaud *et al.* (1994) speculate that FEF fixation cells inhibit the SC fixation cells to allow SC saccade cells to be rapidly prepared for saccade triggering.

The unique feature of our paradigm is that inhibition is required for pro- and antisaccades. If TMS over the right FEF renders inhibition of leftward saccades less efficient, why are there no effects on leftward prosaccades, as here an initial saccade to the LVF stimulus has to be suppressed until after stimulus identification as well? This question is also particularly relevant as prolonged leftward prosaccades were observed in the FEF localizer task. Inhibitory processes might well have been hampered on trials requiring leftward prosaccades in the experimental task; however, it is possible that inhibition does not play an equivalent role in pro- and antisaccades. Inhibition might have more weight on antisaccades, as here a saccade in the opposite direction of the stimulus is required whereas prosaccades are made in the same direction. TMS over the FEF could thus render inhibition processes less efficient, and the effect only observable for antisaccades. With respect to the FEF localizer task, it has to be considered that the requirements are very different. In the localizer task a central arrow instructs saccade direction. In the experimental task the arrow appears in the periphery, leading to the generation of a reflexive saccade programme. This saccade programme has to be inhibited until arrow discrimination, but the presence of such a programme might reduce saccade latencies. In other words, the release of such a programme might be faster than the generation of a volitional saccade, counteracting saccade latency effects on prosaccades.

To conclude, the present study showed that TMS over the right FEF slowed ipsilateral antisaccades. The viable explanations are enhanced attentional engagement, delayed vector inversion or disruption of oculomotor inhibition. The extant evidence favours the latter explanation, as do we. Regardless of which is ultimately correct we have shown that when inhibition is required for pro- and antisaccades, TMS over the right FEF selectively prolongs antisaccade latencies to the RVF.

Notes

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