Involvement of the Supplementary Eye Field in Oculomotor Predictive Behavior

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Abstract

■ The presentation of saccadic and smooth pursuit eye movements as two separate systems has recently been reconsidered: The two subsystems share a number of anatomical structures, and recent data suggest that this sharing also extends to physiological processes. The aim of our study was first to test whether these two subsystems share a common predictive process. We designed a new predictive smooth pursuit paradigm that requires the triggering of unpredictable saccades, performed either during low (ongoing pursuit) or high (pursuit direction reversal) predictive behavior. Saccade latency was used as a probe to reveal a possible sharing of prediction between the two subsystems. The main finding was that saccade latencies were markedly decreased when triggered around pursuit direction reversal and performed in the direction of the predicted pursuit. The aim of the second part of this study was to determine the neural substrate of this common predictive process. According to previous studies, the supplementary eye field (SEF) would be involved in the control of predictive pursuit. The same subjects therefore performed the same tasks, and transcranial magnetic stimulation (TMS) was applied over this area: Decreased saccade latencies were no longer observed, whereas it continued to be observed when applied over the occipital cortex. These results are consistent with (1) The existence of a common predictive process shared by both oculomotor subsystems; (2) The view of the SEF not as a primary oculomotor area but as a higher order structure able to elaborate complex processes, such as prediction, independently of the oculomotor output. ■

INTRODUCTION

Prediction is of major importance in everyday life and may influence a wide variety of behavior. Depending on the processing on which it is exerted, different cognitive aspects of prediction can be determined. Prediction in the sensory–motor domain is critical for a wide variety of functions, such as motor learning or sensory–motor plasticity (Schultz & Dickinson, 2000), and may be evaluated by tracking tasks. The external sensory input is most often visual and the motor output may involve various combinations of limb and eye movements. In the oculomotor system, different components of a tracking behavior may be assessed whether smooth pursuit and/ or saccadic eye movements are required (Leigh & Zee, 2006). In a smooth pursuit task, predictable target motion allows eye and target velocities to be more accurately matched. The predictive pattern may consist of a simple, constant target velocity, or be more complex, such as predictable direction reversal. In the first cycles of smooth pursuit, visual error briefly increases at direction reversal, but the regularity of this phenomenon rapidly allows the subject to anticipate direction reversals (Stark, Vossius, & Young, 1962; Westheimer, 1954). In the saccadic system, any regular pattern in the timing of the target's displacement rapidly alters saccade latencies and leads to the generation of anticipatory saccades, that is, saccades generated before target appearance (Ross & Ross, 1987; Bronstein & Kennard, 1985; Findlay, 1981). The anatomy of this higher-level prediction for smooth pursuit and saccades is thought to involve cortical areas in the frontal lobe (Simo, Krisky, & Sweeney, 2005; Fukushima et al., 2004; Pierrot-Deseilligny et al., 2003; Fukushima, Yamanobe, Shinmei, & Fukushima, 2002; Gaymard, Ploner, Rivaud-Pechoux, & Pierrot-Deseilligny, 1999; Heinen & Liu, 1997; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994; Keating, 1991; MacAvoy, Gottlieb, & Bruce, 1991).

In natural behaviors, ocular tracking is usually performed with a harmonious combination of smooth pursuit and saccades. Although these two oculomotor subsystems were initially thought to be anatomically segregated, increasing evidence for shared neuronal networks has been recently accumulating. A close relationship between anatomical structures controlling each of these two types of eye movements has been found not only at downstream levels, for instance, in the brainstem (Keller & Missal, 2003) and the superior colliculus

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(Krauzlis, 2003), but also at subcortical and cortical levels (Lynch & Tian, 2005). Moreover, recent studies have proposed that these two oculomotor subsystems may share common physiological processes such as the encoding of visual error, attention, or memory (for a review, see Krauzlis, 2005). It may therefore be hypothesized that oculomotor prediction could also be controlled at an upstream, "supramodal" level, hierarchically above both oculomotor subsystems. A first support for this hypothesis was recently suggested by a study in which a general context allowing motor preparation influenced both smooth pursuit and saccade triggering (Joiner & Shelhammer, 2006). However, such a result does not necessarily imply that a common process controls prediction in both oculomotor subsystems because it may be argued that a predictive context could independently but simultaneously influence the two subsystems.

The rationale of the present study was twofold: (1) to test the hypothesis of a common supramodal process controlling prediction in both oculomotor subsystems; and (2) to determine its neural basis. In order to test the first hypothesis, we designed a new paradigm in which predictive pursuit and nonpredictable visually guided saccades were associated. The rationale of this task was to utilize saccade latency as a probe to investigate a possible sharing of prediction between the pursuit and the saccadic systems. The pursuit task consisted of following a target moving at a constant velocity with regular, that is, predictable, direction reversals. Trials comprised an unpredictable number of cycles. At the end of some trials, a visually guided saccade was required, either during linear pursuit (i.e., when no high-level prediction is required), or at the time of direction reversal (i.e., when high-level prediction is required). We reasoned that if high-level predictive behavior acquired during smooth pursuit reversal is systematically and automatically shared with the saccadic system, then saccade latencies should be altered when triggered during periods of high predictive behavior. More precisely, saccades should exhibit decreased latencies when triggered toward the predictable pursuit direction.

For our second hypothesis, we reasoned that if the saccadic and the pursuit systems do indeed share a common predictive function, then inhibition of a region assumed to be involved in prediction during pursuit should also affect saccadic latencies. In other words, we speculated that facilitation of saccade triggering observed during critical time intervals of predictive pursuit should be disturbed if a cortical area, involved in predictive control, is inhibited at these critical epochs. It is currently accepted that two frontal cortical areas are critical for high-level prediction during pursuit: the supplementary eye field (SEF), in the dorsomedial prefrontal cortex (DMPFC) (Heinen & Liu, 1997), and the frontal eye field (FEF) (Rosano et al., 2002; Schmid, Rees, Frith, & Barnes, 2001; O'Driscoll et al., 2000; Bermann et al., 1999; Petit, Clark, Ingeholm, & Haxby, 1997; Heide, Kurzidim,

& Kompf, 1996; Lekwuwa & Barnes, 1996; Morrow & Sharpe, 1995). Functional differences in predictive behaviors between the SEF and FEF have recently been proposed. In primates, single-cell recordings showed that, in contrast to most FEF neurons, most neurons in the SEF did not exhibit visual responses to target motion (Fukushima et al., 2004). Thus, the SEF involvement in pursuit prediction appears to be more in motor planning than in sensory or perception aspects. Some SEF neurons were found to discharge slightly in advance of direction reversal, a finding compatible with a role of this area in prediction during pursuit (Heinen & Liu, 1997). In support of this result, a recent transcranial magnetic stimulation (TMS) study in humans showed different effects of SEF and FEF stimulation during a periodic pursuit task, the predictive role of the SEF being primarily for direction reversal (Gagnon, Paus, Grosbras, Pike, & O'Driscoll, 2006).

Several lines of evidence suggest that the SEF influences the oculomotor system at a high cognitive level (Nachev, Rees, Parton, Kennard, & Husain, 2005; Amador, Schlag-Rey, & Schlag, 2000; Stuphorn, Taylor, & Schall, 2000; Schlag-Rey, Amador, Sanchez, & Schlag, 1997; Chen & Wise, 1995). This area therefore appeared to be a possible candidate for a "supramodal" control of prediction, for both the pursuit and saccade systems. In order to test this hypothesis, TMS was applied over the putative SEF area immediately before direction reversal. Because SEF lesions in humans result in increased predictable pursuit latency (Heide et al., 1996) and because single-pulse TMS over the SEF exerts mainly inhibitory effects (Drew & van Donkelaar, 2007; Tobler & Müri, 2002; Müri, Rivaud, Vermersch, Leger, & Pierrot-Deseilligny, 1995; Müri, Rösler, & Hess, 1994; but see Gagnon et al., 2006), we expected that predictive facilitation, illustrated by decreased PRED saccade latencies, would no longer be observed in trials with SEF inhibition.

METHODS

Subjects

Five healthy, right-handed subjects (3 men, 2 women) with normal or corrected-to-normal vision (range = 27 to 48 years; mean = 38) participated in the experiments, three of them being completely naïve. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

Eye Movement Recordings and Stimuli

Eye movements were recorded by direct-current electrooculography with bitemporal electrodes, in complete darkness, with the head immobilized at the temples. Data were sampled at 200 Hz and stored for off-line analysis. Visual stimuli were presented on a ramp, placed

85 cm in front of the subjects, embedded with contiguous light-emitting diodes (LEDs) subtending a visual angle of 0.18° and with a luminance of 5 cd/m². In the pursuit tasks, apparent target motion was produced by flashing contiguous LEDs in sequence. Thus, target velocity depended on the time each LED remained lit (e.g., 25 msec for a 20 deg/sec pursuit task). The electrooculography system had a resolution of 0.5°. A recording session began with a dark adaptation period of about 10 min, and was then followed by a calibration session in which subjects were asked to look at ±30° visual lateral targets.

TMS Procedure

A MagStim high-speed stimulator (MagStim, Wales, UK) was used and single pulses were delivered with a round coil (diameter: 120 mm). Output was set at 70% of maximum output, exceeding the individual motor resting threshold by 20–30%. In order to influence both SEFs, TMS was applied between the two putative SEF regions, and, as a control condition, over the occipital cortex. Stimulations at these two sites were performed during two different sessions.

The location of a cortical area on the skull is determined by its x (lateral) and y (anteroposterior) coordinates, according to Talairach and Tournoux (1988). The x-coordinate of the SEF area is easily localized because it corresponds to the sagittal line (x = 0). In order to accurately position the coil along the y-axis, we used two complimentary methods. First, we used the international 10–20 EEG System (Herwig, Satrapi, & Schönfeldt-Lecuona, 2003): A previous TMS study has localized the SEF by fMRI using a smooth pursuit paradigm (Gagnon et al., 2006), and found that it corresponds to a location just anterior to Cz (Okamoto et al., 2004). Second, it has been shown that the FEF and the SEF have roughly similar y-coordinates (e.g., Gagnon et al., 2006; left FEF: $y = -7$; left SEF: $y = -6$). The FEF has a remarkably consistent location on this axis, and is located 2 cm anterior to the hand primary motor area (Yamamoto et al., 2004; Paus, 1996). We therefore determined, with suprathreshold TMS, the location of the hand motor area and moved 2 cm rostrally. We checked that, in each subject, we obtained similar y-coordinates with these two methods. In order to minimize as best as possible the stimulation of other nearby cortical areas, we positioned the coil with the handle pointing backward and upward, as the surface of the stimulated cortical area has been shown to rapidly shrink when the distance between the coil and the surface of the skull increases (Walsh & Pascual-Leone, 2003). During SEF stimulations, we confirmed that no motor twitches in either hand and no blinks were observed. For occipital stimulation, the coil was positioned over the occipital cortex (3 cm above Oz), with the handle pointing backwards. During both conditions, the coil was held by the examiner.

Oculomotor Paradigms

Smooth Pursuit Experiments

In all smooth pursuit experiments, subjects were instructed to follow as accurately as possible a pursuit target that moved at a constant velocity over a horizontal 30° range. The target initially appeared during 1500–2000 msec at 0° (i.e., straight ahead), then started to move towards a right or left 15° position. At this point, its direction reversed, and it immediately started to move toward the opposite 15° position. A trial consisted of 4 to 8 hemicycles.

First pursuit task: Predictable pursuit − unpredictable saccades. The target moved at a constant 20 deg/sec velocity, and a trial ended when the target reached either the 0° position (mid-position trials) or a lateral ±15° position (direction reversal trials) (Figure 1). At the end of 75% of these trials, a lateral target appeared simultaneously at a location that required a ±10° visually guided saccade. Thus, in mid-position trials, it appeared at ±10°, and in direction reversal trials, it appeared

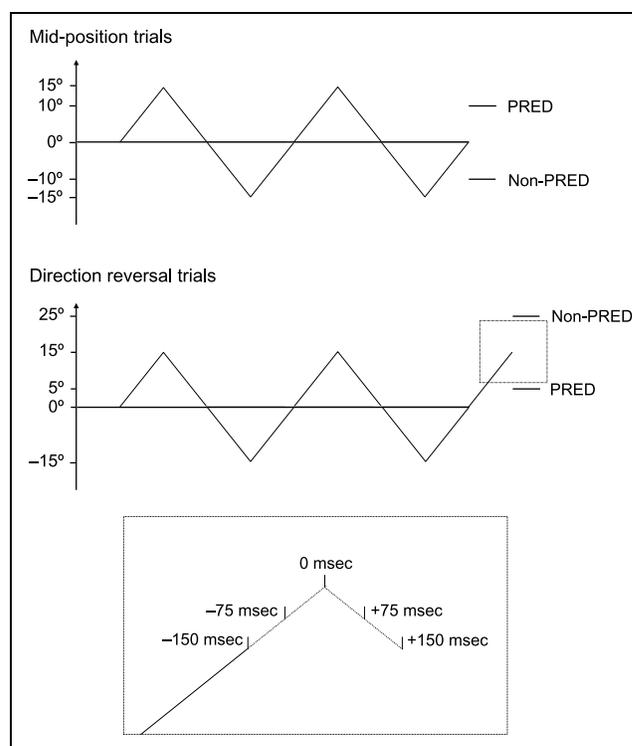**Figure 1.** Predictable pursuit − unpredictable saccade task. Trials ended randomly either at 0° position (mid-position trials) or at ±15° (direction reversal trials). A subsequent target was then presented such that it elicited a saccade performed either in a predictable direction (PRED), that is, in the direction of the ongoing or in the predicted pursuit target direction, or in a nonpredictable direction (non-PRED), that is, in the direction opposite to the ongoing or to the predicted pursuit target direction. In direction reversal trials, targets were presented pseudorandomly either slightly before (−150 msec, −75 msec), at (0 msec), or slightly after (+75 msec, +150 msec) pursuit target direction reversal (inset). Pursuit target disappeared simultaneously with saccade target onset.

either at $-25°$ or $-5°$ (when pursuit ended at $-15°$) or at $5°$ or $25°$ (when pursuit ended at $15°$). Saccades were therefore triggered either in the direction of the ongoing (mid-position trials) or predicted (direction reversal trials) pursuit direction, or in the opposite direction, defining as either PRED (same direction) or non-PRED (opposite direction) saccades. Target position and occurrence were semirandomized in order to allow an equal number ($n = 25$) of each saccade type (rightward and leftward, PRED and non-PRED) to be collected. It should be noted that, in this task, saccade target occurrence was highly unpredictable because it could either not appear or appear under six different conditions and after a variable number of hemicycles. Mean latencies and standard deviations (SD) were determined for each saccade type.

Second pursuit task: Saccades at pursuit direction reversal. In a version of the 20 deg/sec pursuit task, we concentrated on a short period extending from 150 msec before to 150 msec after pursuit direction reversal. The saccade target was presented during this critical epoch, either slightly before (-150 or -75 msec) or slightly after (75 or 150 msec) the pursuit target reached the $\pm 15°$ position (Figure 1). In all conditions, the saccade target location required a $\pm 10°$ saccade, and the pursuit target was systematically turned off at saccade target onset. Timing and right or left location of the saccade target were pseudorandomized, such that a total of 25 saccades were collected in each condition and in each subject for the analysis of mean saccade latencies and SD.

Control Experiments

First control task: Unpredictable pursuit reversal – unpredictable saccades. The rationale for this task was to avoid any predictive behavior. The conditions were similar as in the first pursuit task, except that pursuit reversal occurred at various target positions, being thus unpredictable. Similarly, trials did not systematically end at a lateral $\pm 15°$ position, but at random positions comprised between $2°$ and $12°$, either in the right or in the left hemifield. Twenty-five saccades of each type were collected for the analysis of mean saccade latencies and SD.

Second control task: Slow predictable pursuit – unpredictable saccades. We reasoned that maintaining the fovea on the target at pursuit reversal must become progressively easier as target velocity decreases, therefore requiring less predictive mechanisms (Kao & Morrow, 1994). We therefore used as an additional control condition a task in which the general design was similar to that of the first pursuit task, except that pursuit target velocity was 10 deg/sec. Only direction reversal trials were performed. Twenty-five saccades of each type were collected for the analysis of mean saccade latencies and SD.

Third control task: Saccade task. In our first pursuit task, saccades were triggered either from a central or an excentric position and, in the latter condition, were either centripetal or centrifugal. We therefore ought to verify that these factors did not influence saccade latencies. In this saccade task, a fixation target appeared initially during 1500–2000 msec at $0°$ or $\pm 15°$. A saccade target was then randomly presented $10°$ to the right or left of the fixation target, and subjects were required to look at the saccade target as soon as it appeared. Thus, subjects triggered saccades starting from the same initial orbital position and with same amplitude as in the pursuit tasks. We collected a total of 25 saccades in each condition and in each subject for the analysis of mean saccade latencies and SD.

TMS Experiments

For the TMS experiments, subjects performed the same paradigm as in the second pursuit task (saccades at pursuit reversal), except that the saccade target was always presented at 0 msec (i.e., at the time of pursuit target direction reversal). Based on the results obtained in the first part of our study, we chose to apply TMS at -75 msec, that is, when the largest difference between non-PRED and PRED saccade latencies was observed. A total of 25 saccades were collected in each condition and in each subject, at each stimulation site.

Data Analysis and Statistics

Saccades initiation was determined by visual inspection. They were easily detected during ongoing pursuit because target velocity did not exceed 25 deg/sec, and were even more easily detected at target direction reversal because eye velocity was close to zero at this time (Figure 2).

Statistics

To test whether latencies of both PRED and non-PRED saccades differed between left direction reversal and right direction reversal, statistical analysis was done using a Kruskal–Wallis test. Then, a Kruskal–Wallis test was also used to analyze whether latencies of PRED and non-PRED saccades differed. To compare PRED and non-PRED saccades in the direction reversal and mid-position conditions post hoc analyses were performed using a Mann–Whitney test. To look for significant differences in saccade latencies between all conditions (i.e., -150, -75, $+75$, and $+150$ msec), a Kruskal–Wallis test was performed. Further post hoc analyses were done with a Mann–Whitney test to look for differences between non-PRED and PRED saccade latencies for each condition. A Mann–Whitney test was also used to compare
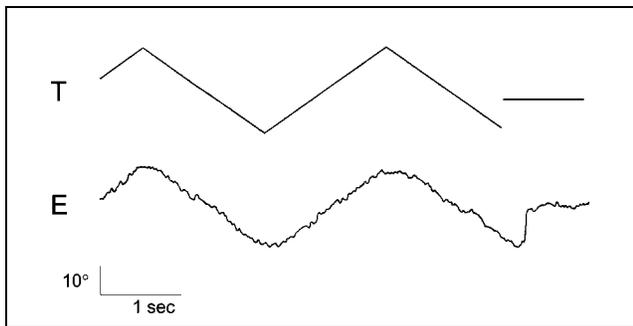
Figure 2. Eye movement data from the predictable pursuit – unpredictable saccade task. Upper trace: target trajectory. Lower trace: recording of eye movement position. Each mark on the *x*-axis corresponds to 10°. Each mark on the *y*-axis corresponds to 1 sec.

non-PRED saccade latencies obtained at mid-position with those obtained at −150, −75, +75, and +150 msec, and to compare PRED saccade latencies obtained at mid-position with those obtained at −150, −75, +75, and +150 msec.

Saccade task. Statistical analysis was performed using a Kruskal–Wallis test to look for differences in the latency of centrifugal and centripetal saccades between the left eccentric and right eccentric conditions. To further examine whether latencies of centrifugal and centripetal saccades at direction reversal and latencies of leftward and rightward saccades at mid-position differed, statistical analysis with a Mann–Whitney test was performed.

TMS experiments. Mean latencies of saccades in the non-TMS condition were calculated for each subject. Latencies obtained with SEF and occipital stimulation were then standardized to the non-TMS values; that is, for a given individual, the percentage increase in saccade latency was calculated for each saccade using the following formula: $100\% \times [(\text{latency TMS/mean latency without TMS}) - 1]$. Thus, a value of 0% means no TMS effect.

To analyze whether TMS had a direction-specific stimulation effect on saccade latencies in each subject (i.e., on leftward or rightward saccades), an analysis of variance (ANOVA) with the dependent variable "latency," the independent variable "direction," and the covariate "subject" was performed. Because there was no significant effect for either "direction" ($p = .295$) or "subject" ($p = .621$), data for leftward and rightward saccades were pooled for further analysis.

To analyze the percentage change in saccade latency for SEF and occipital stimulation, an ANOVA with the dependent variable "percentage" and the independent variables "stimulation" (SEF, occipital) and "side" (non-PRED, PRED) was performed. To evaluate the stimula-

tion effect for the "side," Bonferroni-corrected post hoc comparisons between SEF and occipital stimulation were performed (Statistica 6.0, StatSoft, Tulsa, OK, USA).

RESULTS

Smooth Pursuit Experiments

First Pursuit Task: Predictable Pursuit – Unpredictable Saccades

There was no difference in either PRED or non-PRED saccade latencies between left direction reversal and right direction reversal (PRED: $p = .57$; non-PRED: $p = .22$) and they were therefore pooled for further analysis. The Kruskal–Wallis test showed a statistical difference in the latency of both PRED and non-PRED saccades between direction reversal trials and mid-position trials ($p < .0001$). Further post hoc analysis with the Mann–Whitney test revealed that, in direction reversal trials, latencies of PRED saccades were significantly shorter than those of non-PRED saccades (PRED: mean latency = 190 msec, $SD = 32$; non-PRED: mean latency = 227 msec, $SD = 41$; $p < .0001$) (Figure 3). In mid-position trials, there was no significant difference between PRED and non-PRED saccade latencies (PRED: mean latency = 235 msec, $SD = 63$; non-PRED: mean latency = 246 msec, $SD = 73$; $p = .794$) (Figure 4).

Furthermore, latencies of PRED saccades were significantly shorter in direction reversal trials than in mid-position trials ($p < .0001$), whereas latencies of non-PRED saccades did not differ between the two conditions ($p = .383$).

Second Pursuit Task: Saccades at Pursuit Direction Reversal

The Kruskal–Wallis test showed that there was a significant difference in saccade latencies between the four different time intervals ($p < .0001$) (Figure 4). Post hoc comparisons showed that latencies of PRED saccades were significantly shorter than those of non-PRED saccades when triggered −150 msec (PRED: mean latency = 198 msec, $SD = 32$; non-PRED: mean latency = 220 msec, $SD = 37$; $p = .004$) and −75 msec (PRED: mean latency = 186 msec, $SD = 28$; non-PRED: mean latency = 228 msec, $SD = 35$; $p < .0001$) before expected pursuit direction reversal. A similar result was observed at +75 msec (PRED: mean latency = 189 msec, $SD = 49$; non-PRED: mean latency = 236 msec, $SD = 50$; $p < .0001$) but not at +150 msec (PRED: mean latency = 229 msec, $SD = 55$; non-PRED: mean latency = 242 msec, $SD = 51$; $p = .33$). Further analysis showed that latencies of non-PRED saccades triggered in mid-position trials in the first experiment did not differ significantly from latencies of non-PRED saccades triggered at −150 msec (non-PRED mid-position: mean latency = 246 msec, $SD = 73$;
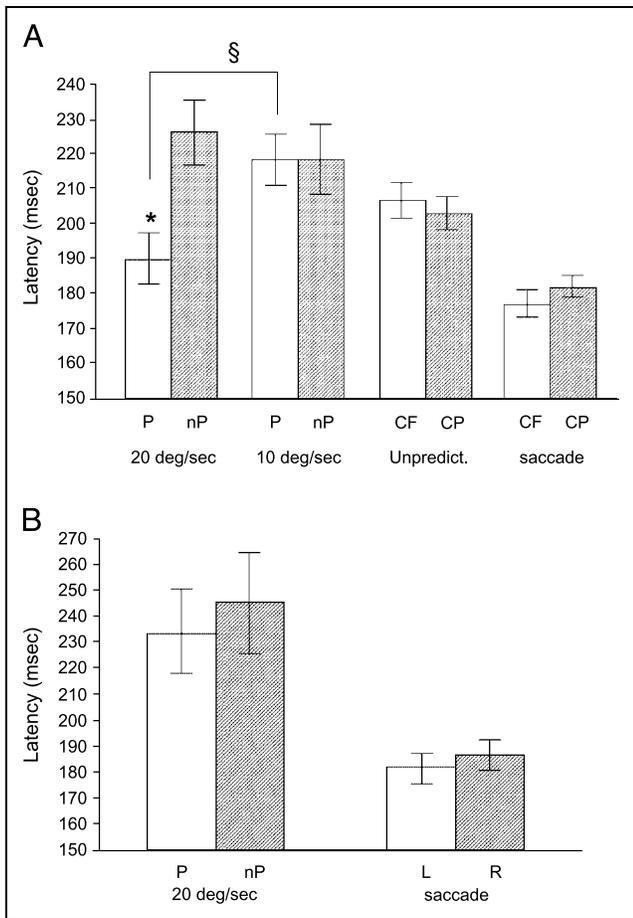
Figure 3. (A) Saccade triggered at ±15°. Latencies (mean and 0.95 confidence intervals) in the predictable pursuit − unpredictable saccade task (20 and 10 deg/sec), in the unpredictable pursuit task (unpredict.) and in the control saccade task. *Comparison between PRED (P) and non-PRED (nP) saccades in the 20-deg/sec pursuit task; $p < .0001$. §Comparison between PRED saccades in the 20-deg/sec and the 10-deg/sec pursuit tasks; $p < .0001$. (B) Saccade triggered at 0°. Latencies (mean and 0.95 confidence intervals) in the predictable pursuit − unpredictable saccade task (20 deg/sec) and in the control saccade task. CF = centrifugal saccades; CP = centripetal saccades; L = left; R = right.

non-PRED = −150 msec: mean latency = 220 msec, SD = 37; $p = .10$), at −75 msec (non-PRED mid-position: mean latency = 246 msec, SD = 73; non-PRED = −75 msec: mean latency = 228 msec, SD = 35; $p = .58$), at +75 msec (non-PRED mid-position: mean latency = 246 msec, SD = 73; non-PRED +75 msec: mean latency = 236 msec, SD = 50; $p = .99$) and at +150 msec (non-PRED mid-position: mean latency = 246 msec, SD = 73; non-PRED +150 msec: mean latency = 242 msec, SD = 51; $p = .62$). Latencies of PRED saccades triggered in mid-position trials in the first experiment (PRED mid-position: mean latency = 235 msec, SD 63) were significantly different from the latencies of PRED saccades triggered at −150 msec (PRED mid-position: mean latency = 235 msec, SD = 63; PRED −150 msec: mean latency = 199 msec, SD = 33; $p < .001$), at −75 msec (PRED mid-position: mean latency =

235 msec, SD = 63; PRED −75 msec: mean latency = 187; SD = 28; $p < .0001$), and at +75 msec (PRED mid-position: mean latency = 235 msec, SD = 63; PRED +75 msec: mean latency = 189; SD = 49; $p < .0001$), but not at +150 msec (PRED mid-position: mean latency = 235 msec, SD = 63; PRED +150 msec: mean latency = 229, SD = 55; $p = .64$).

Control Experiments

First Control Task: Unpredictable Pursuit Reversal − Unpredictable Saccades

Because target direction reversal was totally unpredictable in this task, we compared centrifugal and centripetal saccade latencies. No statistical difference was found between both values (centripetal saccades: mean = 202 msec, SD = 45; centrifugal saccades: mean = 207 msec, SD = 42; Mann–Whitney = 0.08) (Figure 3).

Second Control Task: Slow Predictable Pursuit − Unpredictable Saccades

Because latencies of both PRED and non-PRED saccades did not differ between left direction reversal and right direction reversal (PRED: $p = .057$; non-PRED: $p = .55$), they were pooled for further analysis.

There was no significant difference between non-PRED and PRED saccade latencies in direction reversal trials ($p = .99$) (Figure 3).

Further analysis showed that latencies of PRED saccades triggered during the 20 deg/sec pursuit task were significantly shorter than in the 10 deg/sec pursuit task (PRED 20 deg/sec: mean latency = 190 msec, SD = 32; PRED 10 deg/sec: mean latency = 220 msec, SD = 30; $p < .0001$) (Figure 3). In contrast, latencies of non-PRED saccades did not differ in the 20 deg/sec and the 10 deg/sec pursuit tasks (non-PRED 20 deg/sec: mean latency = 227 msec, SD = 41; non-PRED 10 deg/sec: mean latency = 220 msec, SD = 39; $p = .48$).

Third Control Task: Saccade Task

There was no statistical difference in the latency of centrifugal or centripetal saccades between the initial left and right eccentric orbital positions (centrifugal right vs. left: $p = .113$; centripetal right vs. left: $p = .122$). Thus, for further analysis, saccades obtained in both initial left and right eccentric positions were pooled and named eccentric saccades. Latencies of centrifugal and centripetal saccades obtained in the eccentric condition did not significantly differ (centrifugal: mean latency = 182 msec, SD = 25; centripetal: mean latency = 178 msec, SD = 31; $p = .07$) (Figure 3). Latencies of leftward and rightward saccades in the mid-position condition were also not significantly different (leftward: mean latency =

Figure 4. Saccades triggered at 0° and ±15°. Saccade latencies (mean and 0.95 confidence intervals) in the predictable pursuit − unpredictable saccade task with different time intervals. Comparison between PRED (solid line) and non-PRED (dashed line) saccade latencies; *$p = .004$; **$p < .0001$. Comparison between PRED saccades triggered at 0° and PRED saccades triggered at ±15°, and between non-PRED saccades triggered at 0° and non-PRED saccades triggered at ±15°. §$p < .001$; §§$p < .0001$.
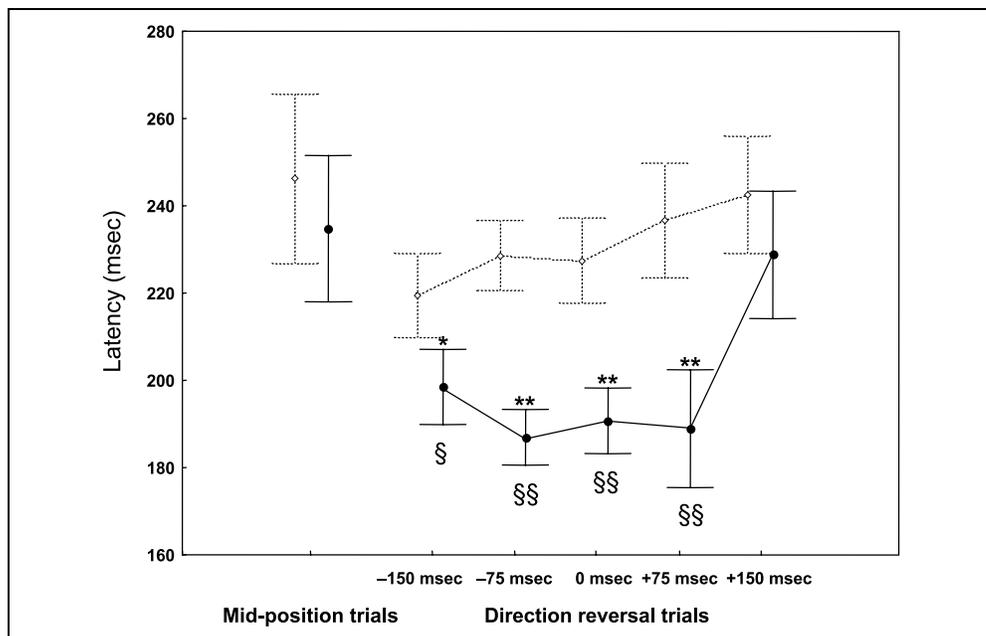
182 msec, $SD = 31$; rightward: mean latency = 187 msec, $SD = 30$; $p = .203$) (Figure 4).

TMS Experiments

Statistical analysis using ANOVA showed significant main effects of stimulation site (SEF and occipital) ($p < .0001$) and non-PRED and PRED directions ($p < .0001$) and a significant interaction between stimulation site and non-PRED and PRED directions ($p < .0001$). Bonferroni-corrected post hoc comparisons showed significant differences between the percentage change in latency of

PRED saccades "SEF" (mean = 24%, $SD = 25$) and non-PRED saccades "SEF" (mean = 3%, $SD = 22$; $p < .0001$), and between PRED saccades "occipital" (mean = 0.5%, $SD = 19$; $p < .0001$) and non-PRED saccades "occipital" (mean = −2.5%, $SD = 16$, $p < .0001$).

The mean percentage change in saccade latency is shown for each subject in Figure 5 and for the whole group in Figure 6.

DISCUSSION

Healthy subjects performed a smooth pursuit task with predictable direction reversal and were required to
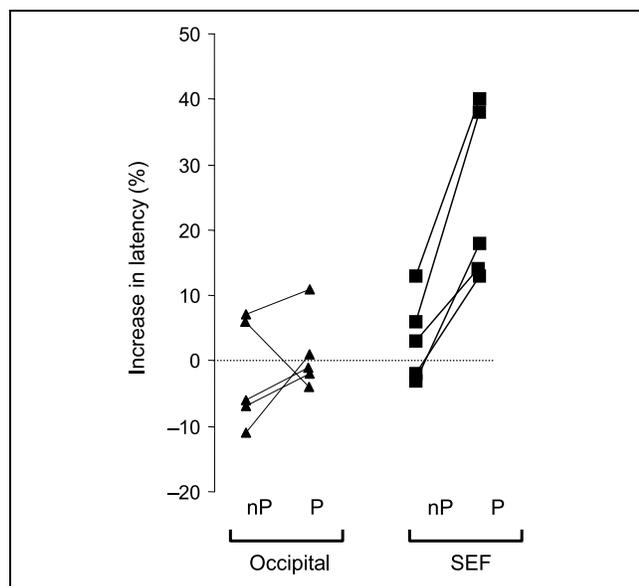

Figure 5. Individual TMS effects. Increase of saccade latency (%) after occipital (triangles) and SEF (squares) stimulation for PRED (P) and non-PRED (nP) saccades for each of the five subjects.
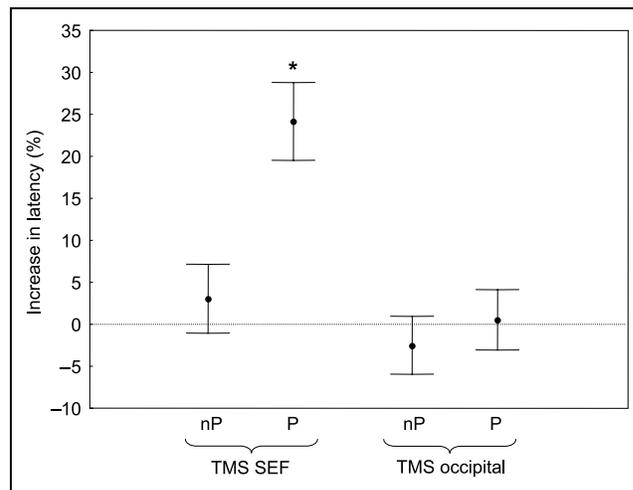

Figure 6. Global TMS effect. Comparison of percent change in latency of PRED saccades "SEF" versus non-PRED saccades "SEF," PRED saccades "occipital," and non-PRED saccades "occipital": nP = non-PRED saccades; P = PRED saccades. For each comparison, *$p < .0001$.

trigger visually guided saccades toward a peripheral target that was presented with unpredictable timing and location. We analyzed saccade latencies and compared saccades triggered in the direction of the ongoing pursuit or in the predicted pursuit direction after target direction reversal, called PRED saccades, and saccades triggered in the direction opposite to the ongoing pursuit or opposite to the predicted pursuit direction after target direction reversal, called non-PRED saccades. The main finding of the first part of the study is that a marked asymmetry between PRED and non-PRED saccade latencies appeared for saccades triggered during a critical epoch extending from slightly before to slightly after pursuit target direction reversal. Shortening of PRED saccade latency was solely responsible for this asymmetry, and was most pronounced for saccades triggered 75 msec before an expected pursuit target direction reversal. Conversely, non-PRED and PRED saccade latencies were identical when triggered during ongoing pursuit, outside this critical period. These results suggest that a predictive behavior ought to improve pursuit performances and is also able to readily influence the saccadic system. They are therefore consistent with the hypothesis of a supramodal predictive function shared by both oculomotor subsystems. In the second part of the study, TMS was applied during this predictive pursuit task, at the critical -75 msec time. The main result is that the marked asymmetry between the latency of PRED and non-PRED saccades was no longer observed when TMS was applied over the putative SEF area, whereas it remained when TMS was applied over the occipital cortex. This suggests that the SEF may be conceptualized as a key area involved in a supramodal control of oculomotor prediction.

Evidence for a Common Predictive System

In the first part of the study, we found that when subjects expected pursuit direction reversal, they triggered unpredictable saccades with shorter latencies when the predicted pursuit direction and the saccade direction were similar. Theoretically, the resulting asymmetry between non-PRED and PRED saccades could be ascribed to mechanical factors. Because subjects anticipated pursuit target direction reversal, their eyes were already moving in the direction of the saccade target when it appeared in the PRED condition but were moving in the opposite direction when it appeared in the non-PRED condition. If eye velocity was a contributing factor, the greatest asymmetry would have been observed at mid-position trials (i.e., when eye velocity was close to 20 deg/sec). Because non-PRED and PRED saccade latencies were similar in these trials, any involvement of this factor can be rejected. It may also be argued that centripetal and centrifugal saccade triggering was differently influenced by elastic intraorbital forces, centrifugal and centripetal saccades being respectively triggered in the direction of or against elastic forces (Fuller,

1996). This hypothesis may also be rejected because no asymmetry was found between centripetal and centrifugal saccades performed under similar mechanical conditions in the control saccade task. Another factor that may have been responsible for this asymmetry is that targeting saccades were triggered while subjects were possibly about to trigger a corrective saccade. The conjunction of these two processes, preparation of a corrective saccade and a visually guided saccade, would have been synergistic in the case of PRED saccades, leading to reduced saccade latencies, and antagonistic in the case of non-PRED saccades, leading to increased saccade latency. Although corrective saccades were infrequent (in less than 30% of the trials), we nevertheless determined their influence and calculated in the before last trials their time of occurrence with respect to target direction reversal. We found that, over all five subjects, corrective saccades, when triggered, occurred after target direction reversal, with an average delay of 235 msec ($SD = 54$). This rather large value suggests that corrective saccades were most likely prepared *after* target direction reversal. Thus, their processing was unlikely to interfere with the preparation of visually guided saccades triggered toward target presented 75 msec *before* target direction reversal (i.e., in the condition at which we observed the strongest predictive effect). Although it cannot be ruled out that triggering of corrective saccades could have influenced the preparation of saccades triggered later, it should be noted that almost no asymmetry was observed for target presented 150 msec *after* target direction reversal (Figure 3).

Finally, at a more cognitive level, it may be hypothesized that the asymmetry in saccade latency resulted from a covert attentional shift. Indeed, it is now well established that a covert attentional shift reduces subsequent saccade latency if both are performed in the same visual hemifield (valid condition), and increases subsequent saccade latencies if performed in the opposite visual hemifield (nonvalid condition) (Posner, 1980). This explanation seems unlikely for several reasons. Firstly, a smooth pursuit task requires visual attention to be focused on the central visual field (van Donkelaar & Drew, 2002) and saccade targets appeared pseudorandomly. During the short period of pursuit direction reversal, our subjects' attention was therefore most likely focused on the central visual field and not covertly shifted toward the peripheral visual field. Secondly, if a covert shift of attention was the mechanism responsible for the asymmetry, then saccades performed in the opposite direction to that of the attentional shift would have increased latencies. However, we did not observe increased latencies for non-PRED saccades. Thirdly, the influence of covert attentional shifts on saccade latencies requires a large number of trials (over a hundred) to obtain significant differences between valid and nonvalid conditions (e.g., Weber, Dürr, & Fischer, 1998). In the present study, a significant asymmetry in saccade latency was observed

after 25 trials only, suggesting a different and more powerful mechanism. Thus, our results strongly suggest that the decreased PRED saccade latencies resulted from the early activation of a predictive mechanism. Such an assumption is strongly supported by the results obtained in our first control task: No significant difference was found in the latency of centrifugal and centripetal saccades, triggered at target direction reversal, when these direction reversals were unpredictable. Similarly, an additional support for this hypothesis is provided by our second control task, in which no asymmetry in saccade latency was found when target velocity was only 10 deg/sec. In this task, subjects could probably more easily maintain their gaze close to the target at target direction reversal because of a slower target velocity. Although a predictive mechanism could still occur in this task, it was probably less crucial, and thus, not sufficient to influence saccade latency. Earlier studies have shown that prediction during a periodic pursuit task diminishes when target velocity is low (Heinen, Badler, & Ting, 2005; Kao & Morrow, 1994). It may thus be concluded that our smooth pursuit task periodically induced the activation of a predictive system that exerted its influence on both pursuit and saccade systems.

Role of the SEF in Oculomotor Prediction

Based on the temporal dynamics of the influence of predictive smooth pursuit on the saccadic system, we found that when TMS was applied over the putative SEF area, 75 msec before pursuit direction reversal, decreased PRED saccade latencies were no longer observed, resulting in symmetrical non-PRED and PRED saccade latencies. A nonspecific effect of TMS was ruled out by the control condition as similar results were obtained in non-TMS experiments and when TMS was applied over the occipital cortex. It may also be argued that our TMS effect could be ascribed to the combined influence on several frontal structures able to alter an oculomotor behavior, such as the FEF or the pre-SMA. A TMS influence on the FEFs was unlikely in our experiments, according to the position of the coil, pointing backward and upward. Thus, the distance between the coil and the scull in the FEF area was more than 3 cm vertically and 8 cm laterally. According to current knowledge, TMS influence rapidly shrinks as the distance between the coil and the brain increases (Walsh & Pascual-Leone, 2003). In contrast, the pre-SMA was most probably affected by TMS over the SEF area, as both structures are in close vicinity. Although the pre-SMA may be involved in various processes that could influence oculomotor tasks, such as sequence learning (Isoda & Tanji, 2004; Kawashima et al., 1998), the updating of new motor sets (Rushworth, Walton, Kennerley, & Bannerman, 2004) or switching from an automatic to a volitional action (Isoda & Hikosaka, 2007), its influence on oculomotor tasks remains unclear, and no evidence at present suggests that it could be involved in oculomotor prediction. Because our results are consistent with SEF data, we believe that it is reasonable to assign the observed effect to an influence on the "SEF area" although an involvement of the pre-SMA cannot be ruled out.

The temporal dynamics of our effects fit nicely with previous electrophysiological and clinical findings during predictable pursuit eye movements. In the monkey, cells in the SEF were found to progressively increase their discharge rate around the time of pursuit direction reversal, with the initial rise being observed 75 msec prior to direction reversal (Heinen & Liu, 1997). In humans, TMS over the SEF has been shown to affect pursuit velocity when applied 75 msec prior to expected target direction reversal but not during ongoing pursuit (Gagnon et al., 2006), and patients with SEF lesions showed increased latencies of pursuit direction reversal (Heide et al., 1996). In a paradigm of predictable pursuit initiation, the latency of anticipatory pursuit was shortened if electrical stimulation of the SEF started between 275 and 75 msec before pursuit onset (Missal & Heinen, 2001). Interestingly, no movement could be triggered if the animal was not expecting target motion (Missal & Heinen, 2004). The main conclusion of these studies is that the SEF is able to influence smooth pursuit according to endogenous cues, such as in a predictive context.

The role of the SEF in the saccadic system remains poorly understood. This area has many connections with the saccadic system, at cortical, subcortical, and brainstem levels (Huerta & Kaas, 1990; Shook, Schlag-Rey, & Schlag, 1990), and electrophysiological studies have found saccadic activities in the SEF in a large variety of tasks (for a review, see Carpenter, 2004). However, the few available lesion studies in humans failed to reveal basic oculomotor impairments, but have instead revealed cognitive impairments, such as poor task set shifting (Husain, Parton, Hodgson, Mort, & Rees, 2003) and saccade sequence learning (Müri et al., 1994; Gaymard, Pierrot-Deseilligny, & Rivaud, 1990). The view of this area as a high-order structure has been confirmed by brain imaging techniques and by recent electrophysiological data that suggest that the SEF could be involved in reward-predicting activities (Amador et al., 2000), conflict situations (Nachev et al., 2005; Schlag-Rey et al., 1997), performance monitoring (Stuphorn et al., 2000), and conditional learning (Chen & Wise, 1995).

It may therefore be proposed that our predictable smooth pursuit task, especially at 20 deg/sec, induced a periodic SEF activation around the time of direction reversal, related to performance monitoring (avoiding eye lag) and to motor learning, which also influences the saccadic system. In a recent brain imaging study, the SEF was found to be able to influence both saccadic and pursuit systems in a predictive context (O'Driscoll et al., 2000). The SEF thus appears not to be a primary oculomotor area, but rather a higher-order structure able to elaborate complex processes independently of the oculomotor output.

The SEF might exert its influence on the oculomotor system through multiple connections with structures

involved in both smooth pursuit and saccade execution (FEF: Lynch & Tian, 2005; Schall, Morel, & Kaas, 1993; Stanton, Bruce, & Goldberg, 1993; caudate nucleus: Lynch & Tian, 2005; basal ganglia: Parthasarathy, Schall, & Graybiel, 1992; superior colliculus and omnipause neurons: Shook et al., 1990).

Among these multiple levels, the SEF predictive influence could be directly exerted on the FEF. Using a ''free-choice'' saccade task in monkeys, Coe, Tomihara, Matsuzawa, and Hikosaka (2002) showed that SEF neurons started to alter their firing rate earlier than FEF neurons before target presentation. The authors concluded that anticipatory activity reflecting internal decision-making processes for upcoming saccades is generated in the SEF and then transmitted to the FEF. A leading role of the SEF was also suggested by a recent fMRI study in which anticipatory activity for saccade preparation began earlier in the SEF than in the FEF (Connolly, Goodale, Cant, & Munoz, 2007).

Predictive behavior during a pursuit task could be interpreted in terms of a ''time interval model'' (Buhusi & Meck, 2005; Salinas & Sejnowsky, 2001). It has recently been proposed that this concept could also apply to the saccadic system (Joiner & Shelhammer, 2006). Based on the results of a predictive saccade paradigm, the authors suggested that prediction is ''based on an internal timing reference or clock.'' In such a context, the SEF might be conceptualized as a key player in the interval timing of predictive oculomotor tasks. According to this concept, the SEF would thus be analogous, in the oculomotor system, to the pre-SMA/SMA complex for the motor system (Stevens, Kiehl, Pearlson, & Calhoun, 2006; Buhusi & Meck, 2005; Pouthas et al., 2005; Lewis & Miall, 2003; Salinas & Sejnowsky, 2001).

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