

Facilitation of Smooth Pursuit Initiation by Electrical Stimulation in the Supplementary Eye Fields

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Missal, M. and S. J. Heinen. Facilitation of smooth pursuit initiation by electrical stimulation in the supplementary eye fields. *J Neurophysiol* 86: 2413–2425, 2001. The role of the supplementary eye fields (SEF) during smooth pursuit was investigated with electrical microstimulation. We found that stimulation in the SEF increased the acceleration and velocity of the eyes in the direction of target motion during smooth pursuit initiation but not during sustained pursuit. The increase in eye velocity during initiation will be referred to as pursuit facilitation and was observed at sites where saccades could not be evoked with the same stimulation parameters. On average, electrical stimulation increased eye velocity by ~20%. At most sites, the threshold for a significant facilitation was 50 μ A with a stimulation frequency of 300 Hz. Facilitation of pursuit initiation depended on the timing of stimulation trains. The effect was most pronounced if the stimulation was delivered before smooth pursuit initiation. On average, eye velocity in stimulation trials increased linearly as a function of eye velocity in control trials, and this function had a slope greater than one, suggesting a multiplicative influence of the stimulation. Stimulation during a fixation task did not evoke smooth eye movements. The latency of catch-up saccades was increased during facilitation, but their accuracy was not affected. Saccades toward stationary targets were not affected by the stimulation. The results are further evidence that the SEF plays a role in smooth pursuit in addition to its known role in saccade planning and suggest that this role may be to control the gain of smooth pursuit during initiation. The covariance between pursuit facilitation and the timing of the catch-up saccade as a result of stimulation suggests that these different eye movements systems are coordinated to achieve a common goal.

INTRODUCTION

Smooth pursuit eye movements allow primates to follow moving objects with the eyes (for review, see Krauzlis and Stone 1999). If a target of interest starts to move, the eyes accelerate after a short delay (80–100 ms) in the direction of target motion, and eye velocity increases to match target velocity (in ~200 ms). During this smooth eye acceleration, a saccade is often generated to reduce the error between eye and target positions that is introduced by reaction delays in the oculomotor system. The initial eye acceleration during pursuit initiation depends on physical factors like target velocity on the retina and the nature of the visual background (Keller and Khan 1986; Lisberger et al. 1987). In addition to retinal factors, smooth pursuit is influenced by extraretinal factors like attention (Ferrera and Lisberger 1995) and expectation of future target motion (Kowler 1989).

The neural control of visually guided smooth pursuit has been extensively studied, and the role of different subcortical and cortical structures containing neurons active before or during pursuit has been partially elucidated (for reviews, see Keller and Heinen 1991; Krauzlis and Stone 1999). The smooth pursuit pathway has its origin in the motion processing pathway (Beutter and Stone 1998; Komatsu and Wurtz 1989; Lisberger et al. 1987; Tychsen and Lisberger 1986; Watamaniuk and Heinen 1999), a specialized subdivision of the visual system (Ungerleider and Mishkin 1982). This subdivision includes two visual areas in the region of the superior temporal sulcus, the middle temporal (MT) (Albright 1984; Baker et al. 1981; Felleman and Kaas 1984; Maunsell and Van Essen 1983a; Zeki 1974) and medial superior temporal areas (MST) (Desimone and Ungerleider 1986; Maunsell and Van Essen 1983b). Area MT projects to the frontal oculomotor area or frontal eye field (FEF) located in the arcuate sulcus (Ungerleider and Desimone 1986), which is part of a frontal network involved in gaze control (for review, see Schall 1997). A region of the FEF located in the fundus of the arcuate sulcus is involved in the control of smooth pursuit (referred to as FEF_{SEM}; SEM stands for smooth eye movements). Indeed, the FEF_{SEM} contains neurons active before and during smooth pursuit (Gottlieb et al. 1994; MacAvoy et al. 1991). Electrical stimulation in that area has been shown to evoke smooth eye movements (Gottlieb et al. 1993; Tian and Lynch 1996a) and to increase the gain of smooth pursuit (Tanaka and Lisberger 2001).

The involvement of the frontal lobe in smooth pursuit control is probably not limited to the FEF_{SEM}. Area MST, which contains neurons active during pursuit (Newsome et al. 1988), projects to the dorsomedial frontal cortex (DMFC) (Huerta and Kaas 1990; Maioli et al. 1998). It has been shown in the macaque monkey that the DMFC also contains neurons active during smooth pursuit (Heinen 1995; Heinen and Liu 1997). The area of the DMFC where pursuit neurons were found coincides anatomically with the supplementary eye field (SEF). The SEF contains neurons active before saccades and low-current electrical stimulation in the SEF evokes these movements (Russo and Bruce 2000; Schlag and Schlag-Rey 1987). In the Telazol-anesthetized Cebus monkey preparation, Tian and Lynch (1995) showed that smooth eye movements could also be evoked by microstimulation in the SEF. However,

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Russo and Bruce (2000) reported that electrical stimulation in the SEF of the awake macaque monkey does not evoke smooth eye movements. Therefore the role of the SEF during smooth pursuit is still questionable.

The aim of this study was to investigate the role of the macaque SEF during smooth pursuit with electrical stimulation. Electrical stimulation was applied during fixation, smooth pursuit initiation and steady-state pursuit. We found that microstimulation of the SEF during fixation did not evoke smooth eye movements. However, if current was applied during pursuit initiation, an increase in initial eye acceleration and eye velocity was observed. This pursuit facilitation was not observed during steady-state pursuit. Evoked saccades and pursuit facilitation were obtained at different sites in the SEF. The latency of catch-up saccades was significantly lengthened when pursuit was facilitated. The results suggest that besides their known role in saccade preparation, the SEF also contributes to the initiation of smooth pursuit.

A preliminary report of these results has been published previously in abstract form (Missal and Heinen 1999).

METHODS

Surgical procedures

The results reported in the present study were gathered from stimulation made in two adult rhesus monkeys (*Macaca mulatta*; subsequently referred to as *GU* and *SA*). All procedures were approved by the Institutional Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

Surgery was performed under aseptic conditions. Under isoflurane gas anesthesia, a ~ 2 cm craniotomy was trephined in the skull, at anterior position 24 mm in Horsley-Clark stereotaxic coordinates. The craniotomy was centered on the midline of the brain in *monkey GU* and 5 mm right to the midline in *monkey SA*. Bone screws were inserted around the perimeter of the exposed area. A stainless steel recording chamber (Crist Instrument) was positioned over the craniotomy. The chamber was cemented on the skull using rapidly hardening acrylic. A coil of Teflon-coated stainless steel wire was set under the conjunctiva of one eye using the method developed by Fuchs and Robinson (1966). A head-restraint device was positioned on the midline caudally. After surgery, the monkeys were returned to their cage and were allowed to recover fully from surgery. Antibiotics (Ancef) and analgesics (Buprenex) were administered under the direction of a veterinarian during the postoperative period.

At the end of experiments, *monkey GU* was deeply anesthetized with pentobarbital and perfused with a 10% formalin solution, and the brain was removed.

Animal training

Monkeys were trained to pursue a 1° target spot back-projected on a tangent screen located 40 cm in front of the animal that was generated with an analog oscilloscope. Each trial was initiated by the appearance of a target for 400 ms during which the monkeys had to fix at that initial position. After the animal foveated the target, the fixation period lasted for 500 ms. During that period, animals had to maintain gaze within a square electronic window of $4 \times 4^\circ$ centered around the target. At the end of the fixation period, the target stepped to an eccentric position and then started to move at constant velocity ("step-ramp" or Rashbass stimulus) (Rashbass 1961). The target always stepped in the direction opposite that of subsequent target motion. For some experiments, the amplitude of the step was varied to try to obtain saccade free trajectories. This strategy was successful in

monkey SA (example presented on Fig. 1). In *monkey GU*, catch-up saccades were more frequent (see following text, example presented on Fig. 8).

Monkeys were also trained in a fixation task to evaluate the influence of stimulation during fixation of a stationary target. During this task, monkeys were required to maintain their gaze at the position of a spot of light that appeared in the center of the screen or at an eccentric position. A variant of this task, the gap-fixation task, was designed to evaluate the effect of stimulation during fixation in the absence of a visual target. During that task, the target disappeared for 200 or 400 ms at the end of the fixation period. The fixation point reappeared afterwards at the same position it occupied before. The task of the monkeys was to keep fixating the former position of the target until its reappearance.

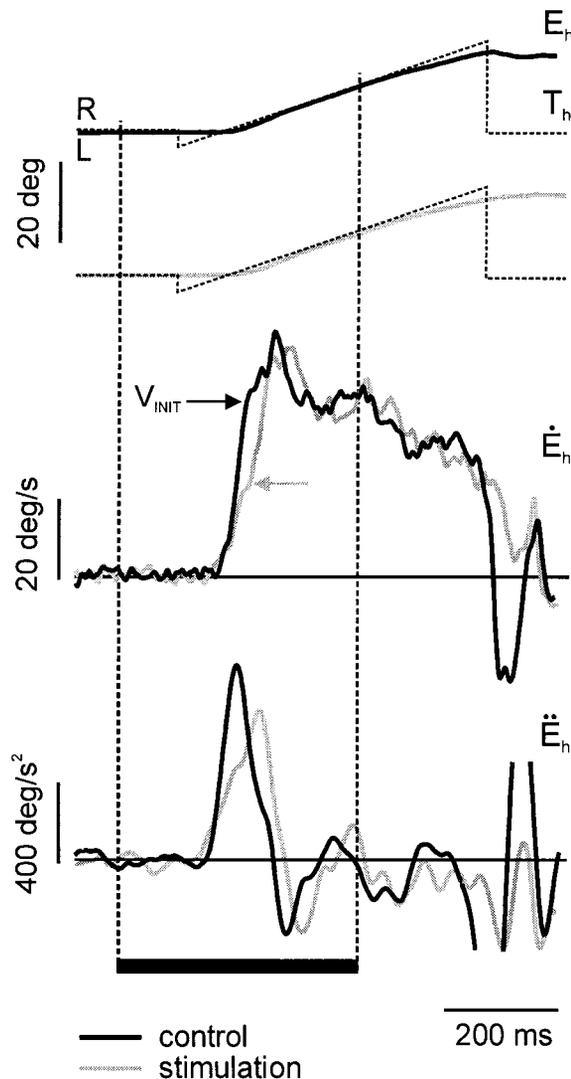


FIG. 1. Example of facilitation of smooth pursuit initiation by stimulation in the supplementary eye field (SEF). From top to bottom: horizontal position of the eye (E_h) and target (T_h), horizontal velocity of the eye (\dot{E}_h , dotted), horizontal acceleration of the eye (\ddot{E}_h , double dotted). Right (R) is up, left (L) is down. Signals are represented by gray traces for the control trial and by black traces for the stimulation trial and are aligned on target motion onset. V_{INIT} : initial eye velocity 50 ms after pursuit onset. The horizontal gray arrow indicates the value of V_{INIT} for the control trial, and the black arrow indicates V_{INIT} during the stimulation trial. The horizontal black bar under the acceleration trace indicates the duration of stimulation (400 ms) and the 2 vertical dashed lines indicate stimulation onset and offset, respectively. Stimulation started 169 ms before pursuit onset (100 ms before target motion onset). Current intensity was $50 \mu\text{A}$ at 300 Hz. Site SA02. Target velocity was $50^\circ/\text{s}$.

Electrical stimulation

Stimulation trains consisted of bipolar pulses (cathodal-anodal) with a duration of 0.2 ms for each phase. Stimulation frequency was usually 300 Hz, and train duration varied between 100 and 400 ms. Current intensity was usually varied between 25 and 200 μA . Stimulation was delivered by a constant current generator through tungsten microelectrodes (impedance, $\sim 1\text{ M}\Omega$; Frederic Haer). Stimulation trains could be triggered at different times with respect to behaviorally relevant events like fixation point onset and offset or target motion onset. Control and stimulation trials were either randomly interleaved in one block or presented in different blocks. These two procedures yielded similar results.

Definition of the supplementary eye fields

We stimulated in the area in the dorsomedial frontal cortex that was previously defined as the supplementary eye fields (SEF), based on saccades evoked by electrical stimulation and neuronal recordings (Schlag and Schlag-Rey 1987). In a preliminary testing, we determined the approximate location of the SEF by stimulation with a current intensity of 50–75 μA at 300 Hz. In the text, SEF corresponds to the functionally defined area and DMFC (dorsomedial frontal cortex) is used to describe the anatomical region.

Data analysis

Vertical and horizontal eye position signals were digitized (1 kHz) and stored on a hard disk for off-line analysis. Horizontal and vertical eye velocity was obtained directly by analog differentiation (with a cutoff frequency of 170 Hz). Matlab and its Signal Processing and Statistical Toolboxes (Mathworks) were used to implement all signal processing and data analysis algorithms. Eye acceleration was obtained by digital differentiation of the eye velocity signal and was filtered using a zero-phase forward and reverse digital filtering procedure (Matlab function `filtfilt`) and a second-order Butterworth filter (cutoff frequency, 25 Hz).

SMOOTH PURSUIT LATENCY. The latency of smooth pursuit (referred to as Lat_{PUR}) was determined on a trial-by-trial basis. The latency of smooth pursuit is the time elapsed between the appearance of the moving target and the increase in eye velocity that characterizes the initial acceleration period. Two independent methods were used to determine latency. The first determined pursuit latency by extrapolation. A segment of the velocity profile during the initiation period was fit with a straight line using linear regression methods. The intersection of that regression line with the baseline velocity level during fixation determined the time at which pursuit started. A similar method has been used previously by other investigators (Carl and Gellman 1987; Krauzlis and Miles 1996). The second method detects latency by determining when acceleration exceeds a threshold fixed at $70^\circ/\text{s}^2$ in *monkey GU* and $150^\circ/\text{s}^2$ in *monkey SA*. Both methods of determination of pursuit latency were visually checked and yielded similar results.

MEASURES DURING PURSUIT INITIATION. During pursuit initiation, eye acceleration increases, reaches a maximum, and then decreases. The maximum acceleration of the eye during that period was measured (referred to as Acc_{MAX}). Eye velocity was measured at a fixed time during initiation, before the catch-up saccade. The latency of the catch-up saccade with respect to pursuit onset was shorter in *monkey SA* (shortest average saccade latency, ~ 100 ms) than in *monkey GU* (shortest average saccade latency, ~ 160 ms). Furthermore, smooth eye acceleration reached a maximum before the saccade. Therefore eye velocity was measured and averaged during the period from 40 to 60 ms after pursuit onset in *monkey SA* and from 80 to 100 ms after pursuit onset in *monkey GU*. This measurement will be referred to as initial velocity or V_{INIT} . The difference in V_{INIT} between control and stimulation conditions will be referred to as ΔV_{INIT} .

The direction of the velocity vector at the time of V_{INIT} was determined by converting horizontal and vertical eye velocity signals from a Cartesian coordinate system into polar coordinates. The elevation angle (referred to as θ) measures the direction of the vectorial velocity at the time V_{INIT} was measured.

LATENCY AND PARAMETERS OF THE CATCH-UP SACCADE. The latency of the catch-up saccade (referred to as Lat_{SACC}) was detected when eye acceleration crossed a threshold of $2,000^\circ/\text{s}^2$ for ≥ 20 ms. A computer program indicated when that threshold was crossed. Saccade offset was detected using the same threshold but starting from a point during steady-state pursuit and moving back in time until the threshold during the deceleration period of the saccade was crossed. After saccade onset and offset were determined, the amplitude of the movement was computed (referred to as Amp_{SACC}).

STATISTICS. Matlab Statistics Toolbox (Mathworks) and Statistica (Statsoft) were used to perform statistical procedures. The significance of all observed effects was tested with parametric methods: Student's *t*-test (referred to as *t*-test) for two-sample comparisons and ANOVA when multiple comparisons were needed. The statistical significance level (*P* level) was always 0.05. All results given in the text are in the form means \pm SE. When necessary, the confidence interval of mean eye velocity during pursuit initiation was computed. The Student's *t* statistics were used to determine the boundaries of the confidence interval of the mean.

RESULTS

Determination of stimulation sites

Sixty-five sites were stimulated in the SEF of two monkeys (38 sites in *monkey GU*, 28 sites in *monkey SA*). During experiments, stimulation was delivered during the fixation and gap-fixation tasks when the eyes were oriented toward different positions in the orbit to assess the possible role of initial orbital eye position on the threshold to evoke a movement. Stimulation was also delivered when the monkey was sitting in a darkened room and not involved in an externally controlled task. Currents used in this preliminary test varied between 50 and 200 μA . Stimulation trains lasted between 100 to 400 ms at 300 Hz. Eye movements were monitored as well as overt behavioral and muscular responses. These procedures were used to determine whether the site of microstimulation was within the neuronal pathway controlling saccades or other movements. The influence of electrical stimulation on smooth pursuit initiation was studied only at sites in the SEF where saccades could not be evoked using the procedures described in the preceding text. Stimulation was delivered at sites where neurons active during pursuit movements were found.

Facilitation of smooth pursuit initiation

We found that at 32 sites, low current electrical stimulation in the region of the SEF during smooth pursuit initiation increased the acceleration and the velocity of the eye in the direction of the moving target. Figure 1 shows an example of a smooth pursuit trial during which the subject (*monkey SA*) had to pursue a target that moved at $50^\circ/\text{s}$ to the right after a step of the target to a position 3° to the left.

In the control situation when no stimulation was applied (gray curves), initial horizontal eye velocity (V_{INIT}) 50 ms after pursuit onset was $25.2^\circ/\text{s}$ and maximum eye acceleration (Acc_{MAX}) was $608.2^\circ/\text{s}^2$. During the stimulated trial (black curves), V_{INIT} was $41.5^\circ/\text{s}$ and Acc_{MAX} was $965.9^\circ/\text{s}^2$. Electri-

cal stimulation lasted for 400 ms, starting 169 ms before pursuit onset (100 ms before target motion onset). Current intensity was $50 \mu\text{A}$ at 300 Hz. This stimulation site was located in the right hemisphere (*site SA02*). It can be seen that low current electrical stimulation produced an increase in maximum eye acceleration and velocity during pursuit initiation, an effect that will be referred to as pursuit facilitation or simply as facilitation. At this site and for this current intensity, average values of V_{INIT} were $28.9 \pm 1.9^\circ/\text{s}$ in controls ($n = 18$) and $34.2 \pm 0.9^\circ/\text{s}$ in stimulation trials ($n = 30$) in a block where stimulation and control trials were interleaved randomly. V_{INIT} during stimulation was significantly different from V_{INIT} in controls ($P = 0.0075$) with the average difference in eye velocity (ΔV_{INIT}) being $5.3^\circ/\text{s}$. Average maximum eye acceleration was $653 \pm 38^\circ/\text{s}^2$ in controls and $753 \pm 26^\circ/\text{s}^2$ in stimulation trials. This difference was also significant ($P = 0.03$). At *site SA02* and in the same block of trials, pursuit latency was $66.2 \pm 2.5 \text{ ms}$ ($n = 18$) during stimulation and $64.1 \pm 1.2 \text{ ms}$ ($n = 30$) in controls. This difference was not statistically significant ($P = 0.41$).

During pursuit facilitation, the direction of the smooth pursuit movement remained unchanged with respect to controls. This was quantified by comparing the direction or polar angle (θ) of the velocity vector at the time V_{INIT} was measured (see METHODS). At *site SA02*, the average value of angle θ was $0.15 \pm 0.60^\circ$ ($n = 18$) in controls and $0.10 \pm 0.50^\circ$ ($n = 30$) in stimulation trials. This difference was not significant ($P = 0.96$). The direction of the velocity vector was compared at nine additional stimulation sites in *monkey SA* and *GU*. The value of θ was compared in blocks of randomly interleaved stimulation and control trials (15–20 trials in each condition). It was found that stimulation did not significantly change the orientation of the velocity vector at any of these sites.

Although electrical stimulation did not change the direction of pursuit, the increase in V_{INIT} might be directionally selective. To test whether V_{INIT} was increased for certain directions only, stimulation was delivered during pursuit in eight different directions spaced by 45° . Each direction was tested independently, with 20 stimulation and 20 control trials randomly interleaved ($60 \mu\text{A}$, 300 Hz, 200-ms train duration). The results are presented on Fig. 2 (*site SA43*). Electrical stimulation increased V_{INIT} in all directions (significant differences are indicated by * in Fig. 2). The largest effect at this site was observed for downward pursuit ($\Delta V_{\text{INIT}} = 10.3^\circ/\text{s}$), and the smallest difference was observed for leftward pursuit ($\Delta V_{\text{INIT}} = 1.6^\circ/\text{s}$). This figure shows the poor spatial selectivity of the facilitation. It is reasonable to suggest that facilitation was omnidirectional for the site presented on Fig. 2. Some directions might show a larger increase in V_{INIT} than others, perhaps due to variations in performance of the monkey. A “tuning curve” like the one represented on Fig. 2 was not built for all sites because of the large amount of data needed (40 trials for each direction). However, during experiments the effect of stimulation was always monitored during both leftward and rightward pursuit. At seven stimulation sites, facilitation was observed for both directions (bilateral facilitation). This observation is consistent with an omnidirectional tuning. For example, at *site GU21*, pursuit initiation was facilitated both to the left (controls: $V_{\text{INIT}} = 11.2 \pm 0.8$; stimulation: $V_{\text{INIT}} = 16.3 \pm 1.1$; $\Delta V_{\text{INIT}} = 5.1^\circ/\text{s}$ or 31%; $P = 0.001$) and to the right (controls: $V_{\text{INIT}} = 11.7 \pm 0.75$; stimulation: $V_{\text{INIT}} = 15.5 \pm$

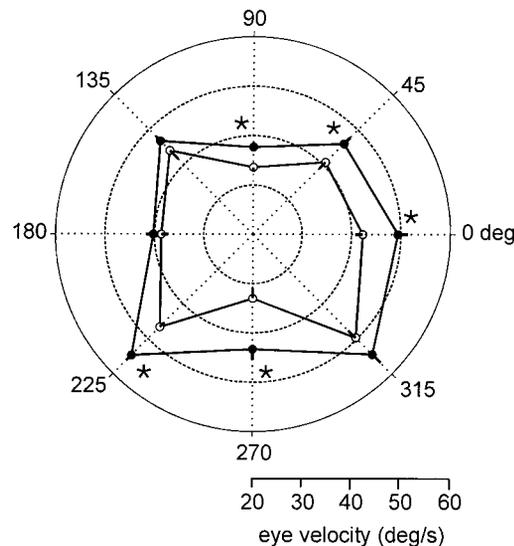


FIG. 2. Polar plot of vectorial eye velocity (radius) as a function of pursuit direction (angle). ●, eye velocity during stimulation trials; ○, eye velocity during controls. Each symbol represent the mean of vectorial eye velocity measured 50 ms after pursuit onset (~15–20 observations in each mean). The SE is represented above or below the mean for clarity. The size of the SE might be smaller than the symbol used to represent the mean. *, significant differences between control and stimulation trials ($P < 0.05$). Note that the origin of the radius axis is $20^\circ/\text{s}$. Current intensity was $60 \mu\text{A}$ at 300 Hz. *Site SA43*.

0.92 ; $\Delta V_{\text{INIT}} = 3.8^\circ/\text{s}$ or 25%; $P = 0.0039$). However, at 17 stimulation sites, facilitation was observed for pursuit directed ipsilateral to the side of the stimulated hemisphere, and at eight sites, facilitation was observed for pursuit directed contralateral to the side of the side of the stimulated hemisphere. Facilitation was therefore mainly ipsilateral with a large proportion of bi- or even omnidirectional effects.

A significant facilitation was observed at 32 sites among the 65 sites stimulated in the two monkeys (32/65; 49%; 20 sites in *monkey GU*, 12 sites in *monkey SA*). On average, ΔV_{INIT} was $5.5 \pm 0.5^\circ/\text{s}$ ($n = 32$). The average difference in Acc_{MAX} was $52.2 \pm 7.2^\circ/\text{s}^2$ ($n = 32$), acceleration during stimulation being larger, except at one site. Figure 3 shows a summary of the facilitation observed for stimulations sites in the two monkeys where a significant increase in V_{INIT} was found. The facilitation was expressed as a percentage increase in eye velocity (Fig. 3A) or maximum acceleration (Fig. 3B) during stimulation trials with respect to controls [(stimulation–control/stimulation)*100]. Each bin contains the number of sites where the labeled increase in V_{INIT} or Acc_{MAX} was observed. Electrical stimulation evoked most frequently an increase in V_{INIT} between 16 and 24% and an increase in Acc_{MAX} between 5 and 25%.

Average pursuit latency was $76 \pm 2 \text{ ms}$ ($n = 32$) in controls and $74 \pm 3 \text{ ms}$ ($n = 32$) in stimulation trials. Pursuit latency was significantly affected only at 3 of 32 stimulation sites (3/32; 9%). The significant difference was independent of the method used to determine Lat_{PUR} . In conclusion, it is reasonable to suggest that electrical stimulation did not alter the time of smooth pursuit initiation.

Stimulation during steady-state pursuit

The effect of microstimulation was also tested after pursuit initiation during the period of constant eye velocity that char-

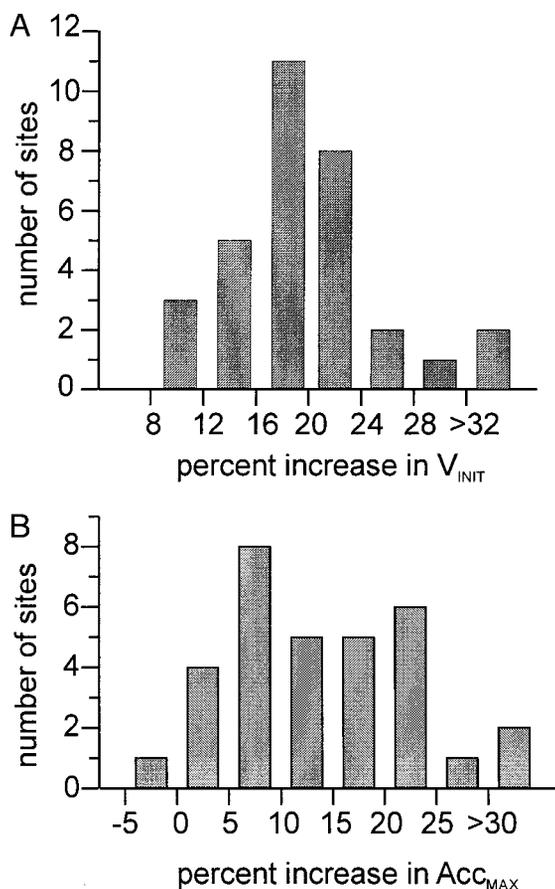


FIG. 3. Summary of the facilitation effect for all sites where a significant effect on V_{INIT} was observed in both monkeys. *A*: percentage increase in initial eye velocity (V_{INIT}). *B*: percentage increase in maximum eye acceleration (Acc_{MAX}).

acterizes steady-state pursuit. Stimulation trains were timed with respect to the onset of target motion. The exact onset time of stimulation trains varied between 300 and 500 ms after target motion onset to start after a potential catch-up saccade. Eye velocity was measured 100 ms after stimulation onset. We found that stimulation during that period did not increase eye velocity as it did during pursuit initiation at the same stimulation sites ($P > 0.05$). This experiment was repeated at seven different stimulation sites and yielded the same negative result: electrical stimulation at sites where initiation was facilitated did not increase eye velocity during ongoing pursuit (7/7 sites). The facilitatory influence of electrical stimulation of the SEF on smooth pursuit was therefore limited to the period of initiation.

Influence of stimulation parameters

Parameters of the stimulation trains that were varied were current intensity, frequency, onset time, and duration. Stimulation frequency was investigated at one stimulation site only. Three different frequencies were tested, 200, 300, and 400 Hz. Current intensity was 75 μA (200-ms train duration). With these parameter, the average ΔV_{INIT} was 5.7°/s at 200 Hz, 12.2°/s at 300 Hz, and 2.6°/s at 400 Hz (20 trials for each category). The largest increase in eye velocity was obtained with a 300-Hz stimulation train.

At 300 Hz, current intensity was varied to determine an

intensity threshold to observe facilitation. In the saccadic domain, a typical definition of an intensity threshold is the current needed to evoke a saccade in 50% of trials. Currents routinely used are 1.5 times the threshold intensity. In the pursuit domain, it is usually difficult to establish a threshold in a similar way as changes in eye velocity are gradual. Current intensity was systematically varied at seven different stimulation sites to determine the minimal or statistical intensity of stimulation trains needed to observe facilitation and characterize the relationship between intensity and facilitation. Figure 4*A* shows an example where a large range of current intensities could be tested. Control trials (\circ) and stimulation trials at different intensities (\bullet) were collected in separate blocks of ~ 20 trials each. Stimulation blocks with different current intensities were randomized in the order of presentation. Stimulation with low current intensities after stimulation with high current intensities still induced smooth pursuit facilitation, indicating that the decreased effect with higher current intensities was not due to tissue damage or lowered electrode impedance. The duration of the stimulation train was 400 ms at 300 Hz. As shown on Fig. 4*A*, a current intensity of 50 μA was sufficient to evoke pursuit facilitation at this site. When the current was further increased, the effect of stimulation increased also. At this site, the relationship between current intensity and V_{INIT} was approximately linear for currents ≤ 100 μA . A maximum increase in V_{INIT} was reached around 200 μA , and larger currents were less effective. The current for which ΔV_{INIT} was the largest

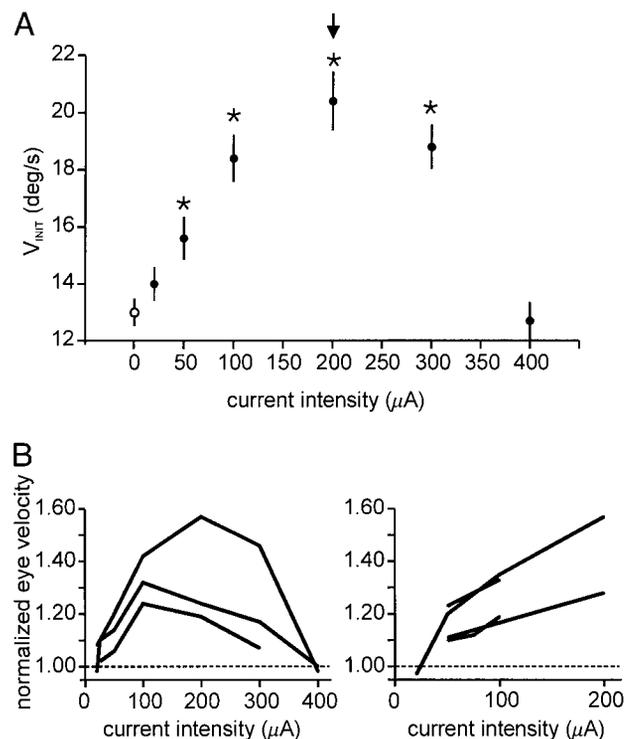


FIG. 4. Relationship between current intensity and facilitation. *A*: example of a single site. \circ , mean of V_{INIT} for control trials (20 observations). \bullet , mean of V_{INIT} for stimulation trials (~ 20 observations at each current intensity). *, a significant difference between stimulation and control trials. \downarrow , the current for which the largest difference between stimulation and control trials was observed (optimal current for this site, GU22). *B*: relationship between current intensity and facilitation for 7 different stimulation sites. Mean eye velocity in stimulation trials was normalized with mean eye velocity in controls (indicated by - - -). *Left*: sites high currents (>200 μA) were tested. *Right*: sites where current intensities ≤ 200 μA were used.

will be referred to as the optimal current at that stimulation site (Fig. 4, \downarrow). At 400 μA , stimulation did not increase eye velocity. To determine the significance of the stimulation effect, a comparison was performed between the different pairs of current intensities and controls. This comparison was achieved with an ANOVA and a post hoc test. Stimulation had a significant effect on V_{INIT} for currents $\geq 50 \mu\text{A}$ but $\leq 300 \mu\text{A}$ [ANOVA; $F(6,133) = 17.04$; $P < 0.01$; LSD post hoc test]. For instance, for the site presented on Fig. 4, V_{INIT} in control trials was $13.0 \pm 0.5^\circ/\text{s}$ ($n = 20$) and $15.6 \pm 0.8^\circ/\text{s}$ ($n = 20$) during stimulation with an intensity of 50 μA . Fifty microamps could therefore be considered as a statistical threshold for the facilitation effect. However, to maximize the facilitation, current intensities routinely used were 75, 100, or maximum 200 μA (at 300 Hz). The influence of current intensity was tested at 7 sites among the 32 sites where a significant pursuit facilitation was observed. At these seven sites, very high current intensities (300–400 μA) were tested only three times (3/7) to not damage the brain tissue. Figure 4B, left, shows stimulation sites where high current intensities were tested. Figure 4B, right, shows stimulation sites where current intensities between 20 and 200 μA were tested. Eye velocity in stimulation trials was normalized with eye velocity in controls. At all sites tested (7/7), the relationship between V_{INIT} and current intensity was linear for current intensities $< 200 \mu\text{A}$.

Median values of V_{INIT} for different current intensities were always close to the mean values, indicating that velocity distributions at different current intensities were symmetric. For the example presented on Fig. 4, the mean of V_{INIT} in controls was $13.0^\circ/\text{s}$ and the median was $13.4^\circ/\text{s}$. For stimulation at 50 μA , the mean was $15.6^\circ/\text{s}$ and the median was $16.6^\circ/\text{s}$. For stimulation at 200 μA , the mean and the median were both $20.4^\circ/\text{s}$. These results suggest that the velocity of each individual movement was increased not just the proportion of exceptionally fast pursuit movements. Indeed, if this were true, it is expected that the mean would be larger than the median.

Temporal relationship between stimulation and facilitation

The effect of stimulation was greater when administered at the end of the fixation period before smooth pursuit began. The influence of the timing of the stimulation train was tested at seven different stimulation sites. Stimulation trains were triggered with respect to the onset of target motion (see METHODS). Figure 5A shows the relationship between the onset of a 200-ms stimulation train and the facilitation effect for one site. The timing of the onset of the stimulation train was varied between 200 ms before target motion onset to 200 ms after target motion onset, in steps of 50 ms. The data are expressed with respect to pursuit onset with zero on the abscissa indicating the onset of pursuit (P_{ON}), which occurred 75 ms after target motion onset on average. Negative values indicate that the stimulation train started before pursuit onset, during the fixation period. A significant facilitation was observed when the stimulation train began between 275 and 75 ms before pursuit onset and was not significant if the stimulation train started 25 ms before pursuit or later. Figure 5B shows all stimulation sites where the influence of the timing of the stimulation train was tested. The left graph shows sites where at least five different onset times were used. The right graph

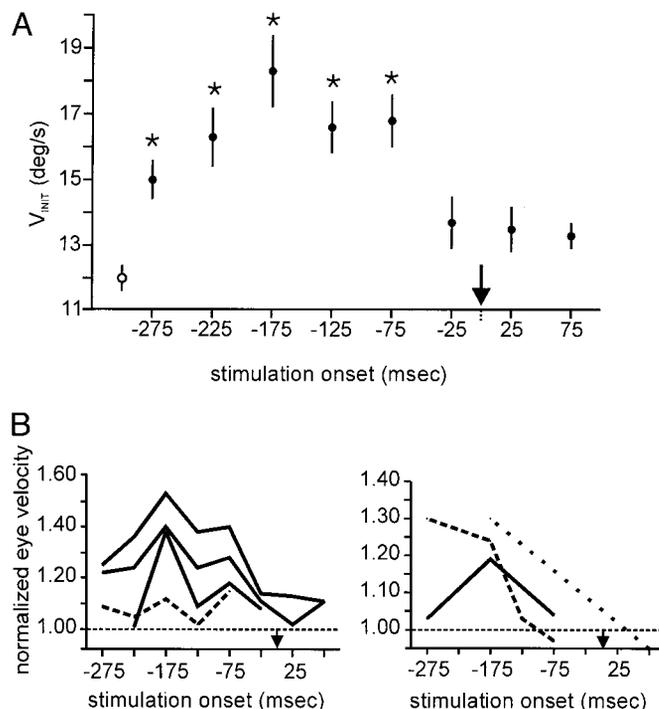


FIG. 5. Relationship between the timing of stimulation onset and facilitation. *A*: example of a single site. The horizontal axis indicates the onset time of the 200-ms stimulation train with respect to pursuit onset (*time 0*, indicated by a vertical arrow). Values of V_{INIT} were grouped in 25-ms bins. Pursuit latency with respect to target motion onset was 75 ms on average. *Site GU22*. Same conventions as on Fig. 4. *B*: relationship between stimulation onset and facilitation for 7 different stimulation sites. Mean eye velocity in stimulation trials was normalized with mean eye velocity in controls (indicated by an horizontal dashed line). Pursuit onset is indicated by a vertical arrow. *Left*: sites where more than 4 different onset times were tested. *Right*: sites where four or less different onset times were used. Continuous lines indicate sites for which the maximum facilitation occurred for a stimulation train starting 175 ms before pursuit onset. The dashed curve shows 2 sites with different optimal onset times (–75 and –275 ms). The dotted line shows a site where only 2 different onset times were used.

shows sites where four or less different onset times were used. Eye velocity in stimulation trials was normalized with eye velocity in controls. Continuous lines indicate sites where the strongest facilitation occurred when stimulation started 175 ms before pursuit onset (indicated by a vertical arrow). Interrupted lines show sites where the maximum effect occurred for different onset times. The dotted curve shows a site where only two different onset times were used.

The latency of the facilitation effect was defined as the time when V_{INIT} became significantly different in stimulation trials compared with controls. This latency could be estimated from the above described time/velocity relationship. If stimulation began 25 ms before pursuit onset, V_{INIT} measured 90 ms after pursuit onset was not significantly increased (time, –25 on Fig. 5; 115 ms after stimulation onset). On the other hand, a significant increase in V_{INIT} was found when stimulation started 75 ms before pursuit onset (time, –75 on Fig. 5). In this condition, the estimated latency is ~ 165 ms ($90 + 75$ ms). Therefore the latency of the facilitation on V_{INIT} with respect to stimulation onset could be between 115 and 165 ms. This estimation is biased by the time at which the measure was made, in the case of *monkey GU*, 90 ms after pursuit onset. This might produce latency measures that are overestimated.

To avoid this limitation, we determined when the velocity of the eye in individual stimulation trials diverged from the mean velocity in controls by using a method based on confidence intervals. Eye velocity in control trials was averaged during the first 150 ms of pursuit initiation and the confidence interval was computed using the Student's *t* statistics (see METHODS). Ten to 20 trials were used to compute the mean and confidence interval of control eye velocity. Ten to 20 individual stimulation trials were compared with that mean. The latency of facilitation was estimated by comparing the time course of eye velocity during pursuit initiation in a single stimulation trial with the average time course in controls. We defined latency as the time when eye velocity in stimulation trials exits the confidence interval of controls and remained out of the confidence interval for more than 50 ms. This last condition was necessary because eye velocity could exit the confidence interval for short periods of time, due to the larger amount of noise present in a single trial as compared with a mean of controls. Figure 6 shows the mean eye velocity (white traces) and the confidence interval of the mean of controls (gray shaded areas) together with the eye velocity of a single stimulated trial (black traces) for two different stimulation sites. In the example presented on Fig. 6A, stimulation started 180 ms before target pursuit onset and lasted for 400 ms. In the example presented on Fig. 6B, stimulation started 67 ms before pursuit onset and lasted for 200 ms. The latency of the facilitation for these single trials is indicated by a vertical arrow above the velocity profile. For the site illustrated on Fig. 6A, this procedure gave an average latency of 56.5 ± 2.1 ms ($n =$

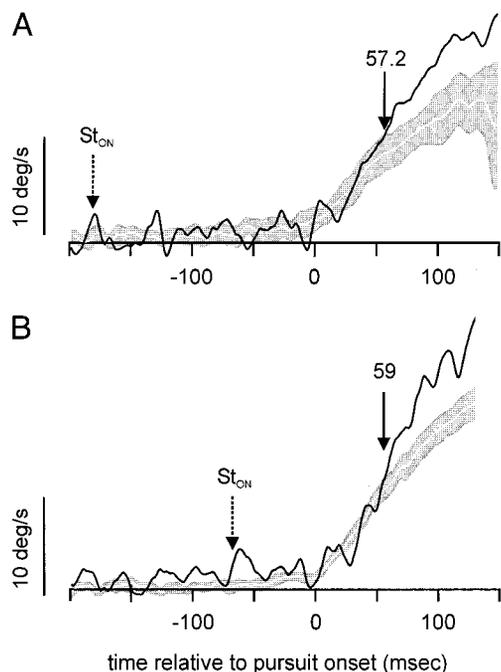


FIG. 6. Latency of the facilitation effect with respect to pursuit onset for 2 stimulation sites. A: stimulation onset (St_{ON} , 1st dashed arrow) was 180 ms before pursuit onset (P_{ON} , vertical dashed line) and lasted for 400 ms until stimulation offset (St_{OFF} , 2nd dashed arrow). The stimulation trial (back curve) is represented on top of the mean (white curve) and confidence interval (shaded gray area) computed from 12 control trials. The solid vertical arrows indicate the time at which the velocity of the eye during the stimulation trial exits the confidence interval of controls. Site *GU54*. B: stimulation started 67 ms before pursuit onset and lasted for 200 ms. Mean and confidence interval computed from 17 control trials. Site *GU51*.

15) with respect to pursuit onset. For the site presented on Fig. 6B, the average latency was 50.6 ± 2.8 ms ($n = 10$). The latencies were similar at the two sites, in spite of the different onset time of the stimulation trains. A similar analysis was repeated at five additional sites. The average latency obtained from all sites tested with this procedure was 61.3 ± 3.5 ms ($n = 7$). This suggests that the facilitation latency does not depend primarily on the onset of stimulation, but on the onset of pursuit. Stimulation of the SEF could alter eye velocity as early as ~ 60 ms after pursuit onset.

Influence of eye velocity

The facilitation during pursuit initiation produced by SEF stimulation could result from either an influence of the electrical stimulation on sensory processes, such as the perception of target motion, or on neuronal processes related to the preparation of the movement. Therefore the facilitation could be related either to target velocity, eye velocity or a combination of both. The influence of eye velocity can be determined if a range of eye velocities can be compared in control and stimulation trials for the same target velocity and stimulation parameters. Figure 7A shows the relationship between average V_{INIT} in controls (abscissa) and stimulated trials (ordinate) for stimulation sites tested in *monkey GU* with the same target velocity ($40^\circ/s$) and stimulation parameters. Each point represents the mean of V_{INIT} in control and stimulation trials for one site. V_{INIT} in controls varied between 10 and $20^\circ/s$. A linear relationship between V_{INIT} in controls and stimulation trials was found (correlation: $r = 0.97$; $P < 0.001$; $n = 15$). Initial eye velocity during stimulation increased with eye velocity in controls. The intercept of the linear relationship was $\sim 1^\circ/s$ and was not significantly different from zero ($P = 0.47$). The slope of the linear relationship was 1.17, showing that the higher the velocity of the eye, the larger was the increment in eye velocity due to stimulation. The main effect of the stimulation, the facilitation effect, resulted of the multiplication of V_{INIT} by a gain factor of ~ 1.2 and not from the addition of a bias. This suggests that electrical stimulation was altering a gain mechanism in the premotor pathway for pursuit.

To investigate the possibility that pursuit facilitation depended on target velocity, a large range of target velocities were tested at the same stimulation site with all other stimulation parameters kept constant. Target velocity was varied between blocks of trials. Stimulation and control trials were randomly interleaved. Figure 7B shows the results obtained at one site, where the largest range of target velocities available could be tested (*monkey GU*; target velocity varying between 5 and $60^\circ/s$ by steps of $5^\circ/s$). The figure shows the relationship between target velocity and V_{INIT} in controls (\circ) and stimulation trials (\bullet). Each point shows the average value and the standard error of V_{INIT} for more than 10 trials. It can be seen that V_{INIT} increased nonlinearly with target velocity. However, for targets moving slower than $30^\circ/s$, the relationship between V_{INIT} and target velocity is approximately linear. When fitted with a linear model, the slope of that relationship was larger in stimulation (0.8) than in control trials (0.6). The different slopes of the relationship between target velocity and V_{INIT} in control and stimulation trials further suggests that electrical

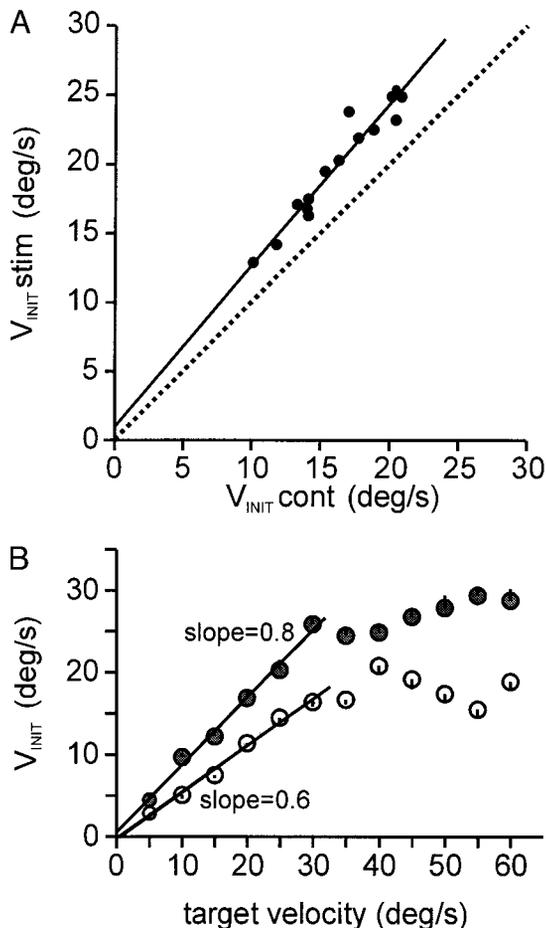


FIG. 7. *A*: relationship between eye velocity in controls ($V_{INIT} \text{ cont}$) and in stimulation trials ($V_{INIT} \text{ stim}$) during pursuit of a target moving at $40^\circ/\text{s}$ for 15 different stimulation sites tested with the same stimulation parameters (*monkey GU*). —, the linear increasing relationship between eye velocity in controls and in stimulation trials. Equation of the regression line: $V_{INIT} \text{ stim} = 1.05 + 1.17 * V_{INIT} \text{ cont}$. \cdots , line is drawn for comparison and has a unit slope and a 0 intercept. *B*: relationship between target velocity and V_{INIT} . ●, mean velocity in stimulation trials; ○, mean for control trials. Each point shows the average of ~ 20 trials. The SE is represented above or below the mean for clarity. The size of the standard error might be smaller than the symbol used to represent the mean. Linear regression lines are represented for controls and stimulation trials for target velocities $\leq 30^\circ/\text{s}$, and their slope are indicated *above* each line.

stimulation was altering a gain mechanism in the premotor pathway for pursuit. Facilitation was weak for low values of V_{INIT} in controls (e.g., for a target moving at $5^\circ/\text{s}$) and was larger when V_{INIT} in controls was higher (e.g., for a target moving at $30^\circ/\text{s}$). For target velocities $30^\circ/\text{s}$, V_{INIT} varied between 15 and $20^\circ/\text{s}$ in controls and varied between 25 and $30^\circ/\text{s}$ in stimulation trials. Higher eye velocities were attained later during the pursuit trial (e.g., in *monkey GU*, maximum eye velocity during pursuit of a target moving at $40^\circ/\text{s}$ was $31 \pm 0.9^\circ/\text{s}$, $n = 17$). The nonlinear relationship between target velocity and V_{INIT} shows that the facilitation was not correlated with target velocity. Indeed, if the facilitation was primarily related to target velocity, it would be expected that V_{INIT} in stimulation trials would continue to increase with increasing target velocities. We conclude that the facilitation does not depend on target velocity primarily, but is a function of the velocity of the eye. The same experiment was repeated at three other stimulation sites and yielded similar results.

Stimulation during fixation

Stimulation was also applied during a fixation task. Pursuits and fixations were collected in different blocks of trials. During the fixation task, the fixation point either remained lit during the whole trial or was temporarily extinguished for 200–400 ms (gap fixation task). The gap fixation task was designed to suppress any retinal slip signal that could interact with the outcome of the stimulation. The initial position of the eye in the orbit was the same as during pursuit trials. Stimulation was applied at the same time with respect to fixation onset with similar current parameters. During fixation trials, smooth eye movements could not be evoked. Similarly, no smooth eye movements were observed if electrical stimulation was delivered during intertrial periods when the animal was spontaneously orienting its gaze toward different positions. These results suggest that the effect of stimulation depended on the motor context at the time of stimulation. Specifically, monkeys had to be involved in a pursuit task for the stimulation to have any observable effect.

Characteristics of the initial catch-up saccade

When a catch-up saccade occurred, its latency (~ 200 ms) was longer than the latency of pursuit (~ 80 – 100 ms). Pursuit facilitation was measured on the smooth eye movement preceding the saccade. Figure 8 shows an example of smooth pursuit facilitation before the occurrence of the catch-up saccade in *monkey GU* (*site 22*, left hemisphere), during the initiation of pursuit toward a target moving to the left at $40^\circ/\text{s}$.

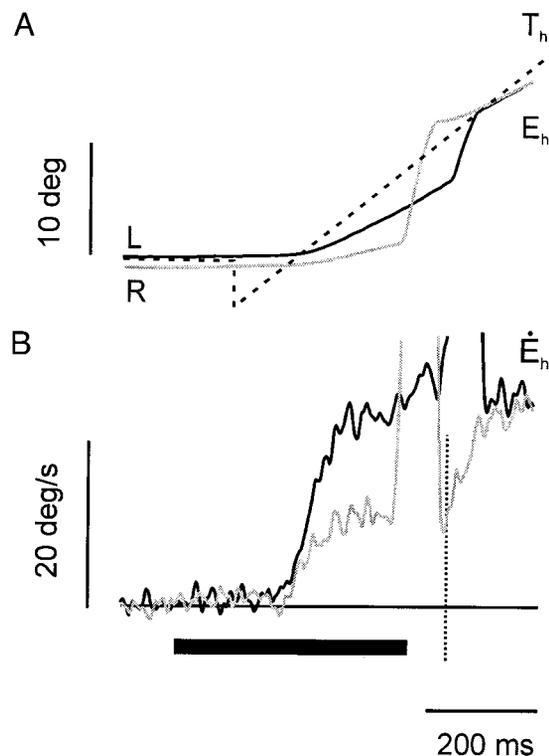


FIG. 8. *A*: example of the effect of pursuit facilitation on the latency of the catch-up saccade. Same conventions as on Fig. 1. Left (L) is up, right (R) is down. Stimulation started 200 ms before pursuit onset. Current intensity was $100 \mu\text{A}$ at 300 Hz (2 times threshold). *Site GU22*. *B*: average values of saccade latency for *site GU22* and for the stimulation sites where catch-up saccades were significantly delayed.

In the control condition (gray curves on Fig. 8), V_{INIT} before the catch-up saccade was $10.7^\circ/s$. In the stimulated trial (black curves on Fig. 8), V_{INIT} was $21.6^\circ/s$. Electrical stimulation lasted for 400 ms and began 100 ms before target motion onset, with a current intensity of $100 \mu A$ at 300 Hz (2 times threshold intensity at this site, see Fig. 4A). On average, eye velocity in controls was 13.0 ± 0.5 and $18.4 \pm 0.8^\circ/s$ during stimulation ($P < 0.001$; $n_1 = n_2 = 20$). As can be seen on Fig. 8, the latency of the catch-up saccade was longer during stimulation trials (230.9 ± 18.9 ms; $n = 20$) than during control trials (156.1 ± 7.5 ms; $n = 19$). This difference was statistically significant (t -test; $P = 0.001$). A similar significant increase in saccade latency was found in 62% of stimulation sites where catch-up saccades were frequent (13/21 sites or 62%; see Fig. 8B). Across all sites, average catch-up saccade latency was 177.1 ± 9.8 ms in controls and 213.1 ± 12.4 in stimulated trials (17% increase on average). The average difference in catch-up saccade latency was as large as 114 ms at one site.

At site *GU22*, in a block of interleaved trials, the amplitude of catch-up saccades was significantly reduced by the stimulation (controls: 7.8 ± 0.2 , $n = 18$; stimulation: 6.2 ± 0.5 , $n = 17$; t -test; $P < 0.05$). However, the position of the eye with respect to the target at the end of the saccade (final error) was not significantly different in control and stimulation trials (controls: 0.3 ± 0.2 , $n = 18$; stimulation: 0.3 ± 0.3 , $n = 17$). In both conditions, saccades were hypometric. Therefore catch-up saccades in stimulation trials were normal and landed near the moving target, except that their occurrence was delayed. As a consequence, the error in position before the saccade was triggered was smaller during stimulation trials.

Saccade delay could be due to current spread to neighboring sites involved in saccade planning due to a competition between the site activated by the electrical stimulus and the site activated by the normal planning of the movement. To test this hypothesis directly, we stimulated the same sites with the same current parameters before saccades of similar amplitudes toward stationary targets. If the increased latency is due to an interaction with neighboring sites involved in saccade control, saccades toward stationary targets should be affected in a similar way as saccades during pursuit. If the delay of the catch-up saccade is specifically due to smooth pursuit facilitation, saccades toward stationary targets should not be affected by electrical stimulation. Therefore at five sites where pursuit facilitation was observed, a control experiment was run during which electrical stimulation was delivered before visually guided saccades toward stationary targets. Current intensity and timing were identical in both pursuit and stationary targets paradigms ($100 \mu A$, 400 ms at 300 Hz). The stimulation train started 100 ms before target onset in both conditions. The amplitude of saccades toward stationary targets was matched with the amplitude of catch-up saccades usually observed during control pursuit trials ($\sim 8^\circ$). Figure 9 shows an example when stimulation preceded the occurrence of saccades toward a stationary target. It was found that electrical stimulation did not delay saccades toward stationary targets at sites where catch-up saccades were delayed during pursuit facilitation. For instance, at site *GU22*, the latency of catch-up saccades in controls was 164.6 ± 7.7 ($n = 22$) and 156.1 ± 4.3 ($n = 17$) during stimulation trials (difference not significant, $P = 0.38$; see Fig. 9B). This experiment was repeated at five sites (controls: 149.8 ± 7.1 ; stimulation: 145.8 ± 13.9 ; $n = 5$; see Fig.

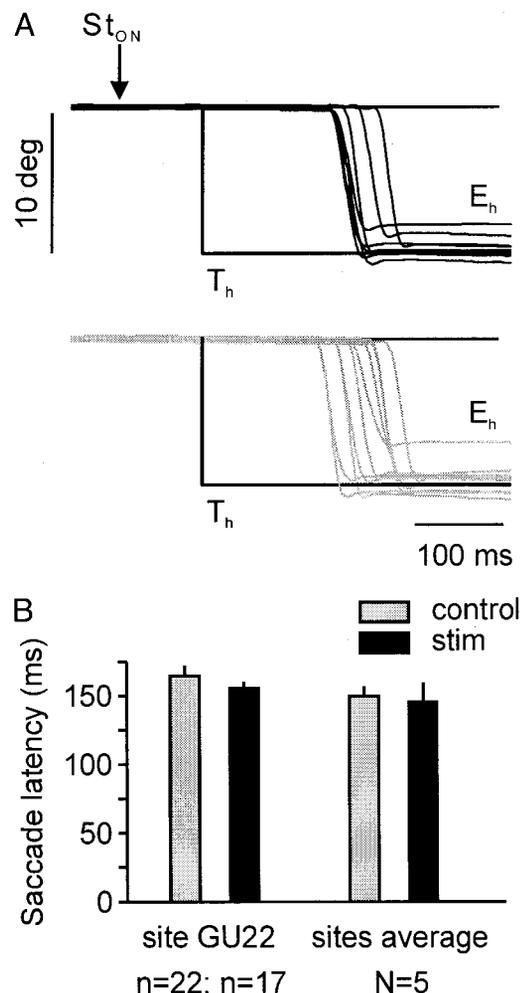


FIG. 9. A: example of saccades toward a stationary target during stimulation (black curves) and controls (gray curves). Same site as on Fig. 8. The stationary target (T_h) appeared 10° in the periphery of the visual field. Stimulation started 250 ms before saccade onset and lasted for 400 ms. Current intensity $100 \mu A$ at 300 Hz. B: average value of saccade latency for site *GU22* and for 5 sites where stimulation before saccades to stationary targets was tested.

9B). The amplitude of saccades toward stationary targets were similar in controls (site *GU22*: 9.1 ± 0.2 , $n = 12$; 4.8 ± 0.2 , $n = 10$) and stimulation trials (8.9 ± 0.2 , $n = 8$; 5.1 ± 0.2 , $n = 9$; $P > 0.05$). Stimulation before saccades toward stationary targets was repeated at four additional sites where saccades during pursuit were delayed. At each site, the latency and metrics of saccades toward stationary targets were unaltered. This result suggests that current spread to neighboring saccadic areas cannot explain the delay that was observed during pursuit.

To reveal whether delayed saccades were due to the higher gain of smooth pursuit initiation observed during stimulation, the effect of current intensity was compared for both phenomena. Figure 10A shows individual traces of the position of the eye as a function of time during control and stimulation trials at site *GU39*. Eye velocity was higher in stimulation versus control trials. Saccade latency increased by 100 ms on average in stimulation trials. At site *GU39*, the optimal current intensity for facilitation was $100 \mu A$. That current was used during the trials presented on Fig. 10. As the velocity of the eye also

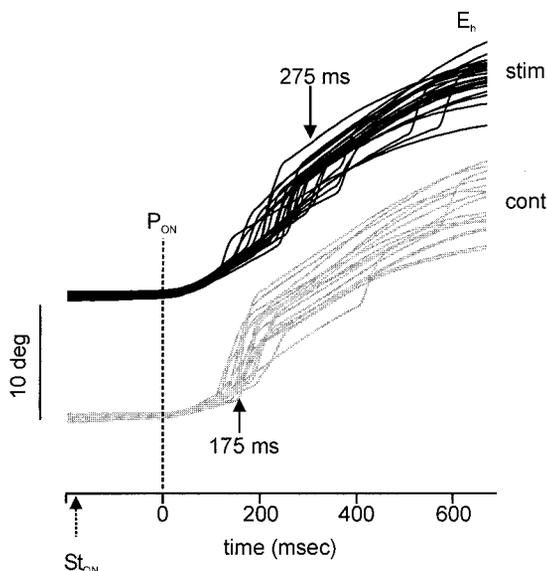


FIG. 10. Example of the effect of pursuit facilitation on the latency of catch-up saccades at site *GU39*. Current intensity was $100 \mu\text{A}$ at 300 Hz (optimal current intensity for this site). The vertical arrows indicate the mean latency of first catch-up saccades. Stimulation started 180 ms before pursuit onset (indicated by an upward dashed arrow) and lasted for 400 ms .

increased with current intensity for intensities $\leq 200 \mu\text{A}$, there could be a correlation between the latency of the catch-up saccade and V_{INIT} . Figure 11A shows the relationship between current intensity and V_{INIT} in controls and stimulation trials for a large range of currents tested at the same site. The same nonmonotonic relationship as described before was found (see Fig. 4). Figure 11B shows the relationship between current intensity and saccade latency for the same site. A significant increase of saccade latency was observed for a current intensity of $50 \mu\text{A}$. Saccade latency increased with current intensity until a maximum was reached at $100 \mu\text{A}$. Larger current intensities caused a progressive return of the latency toward control values. The value of the current for which the strongest effect on saccade latency was observed was similar to the optimal current for facilitation at this stimulation site ($100 \mu\text{A}$). Indeed, the relationship between current intensity and saccade latency was similar to the relationship between current intensity and facilitation (compare Fig. 11, A and B). Therefore the delay of the catch-up saccade covaried with the velocity of the eye during stimulation trials (correlation coefficient: $r = 0.72$, $P = 0.028$, $n = 9$). As V_{INIT} was increased with increasing current intensity, the amplitude of the catch-up saccade was modified appropriately to land near the moving target (Fig. 11C). A similar increase in catch-up saccade latency with increasing current intensity was observed at five additional stimulation sites. Figure 11D shows the average value of normalized saccade latency for these sites. Saccade latency during stimulation trials was normalized with the saccade latency in controls. Saccade latency increased with current intensity for the three intensities tested (50 , 100 , and $200 \mu\text{A}$).

Distribution of pursuit and saccades sites on the cortical surface

Pursuit sites were distributed over the rostrocaudal and lateral extent of the area overlaid by the stimulation chamber,

covering $\sim 1 \text{ cm}^2$ of cortical surface. Figure 12A shows the location of the stimulation chamber in *monkey GU*. The drawing was made from a photograph of the dorsal surface of the brain taken after perfusion. The position that the chamber occupied was clearly visible on the dorsal surface of the brain. The \leftarrow indicates the position of the caudal tip of the arcuate sulcus. Figure 12B shows the distribution of stimulation sites in *monkey GU* projected onto a stereotaxic grid; the \leftarrow indicates the same position as on Fig. 12A. Sites where pursuit facilitation was observed (\bullet) were intermixed with sites where saccades were evoked (\diamond). At two sites, evoked saccades and smooth pursuit facilitation were both observed, but at different depths of the electrode in the track (\blacklozenge). Stimulation sites where no observable effect of the stimulation was found are also represented (\circ). No obvious spatial organization of pursuit or saccade sites was observed. No extensive cortical map-

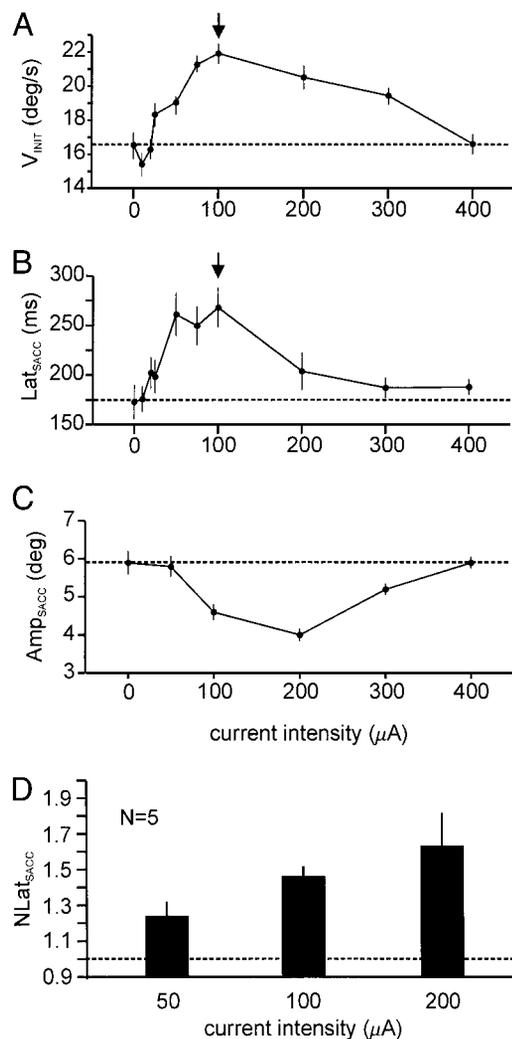


FIG. 11. Influence of current intensity on catch-up saccades parameters. Same site as on Fig. 10. A: relationship between current intensity and V_{INIT} . The smallest current intensity needed to have a significant facilitation effect was $50 \mu\text{A}$. \downarrow , the optimal current intensity for this site ($100 \mu\text{A}$) and the mean of the individual examples shown on Fig. 10. B: relationship between current intensity and catch-up saccades latency (Lat_{SACC}). C: relationship between current intensity and catch-up saccades amplitude (Amp_{SACC}). D: normalized saccade latency ($\text{NLat}_{\text{SACC}}$) for 3 different current intensities tested at 5 sites. ---, the average value of controls for the different variables measured.

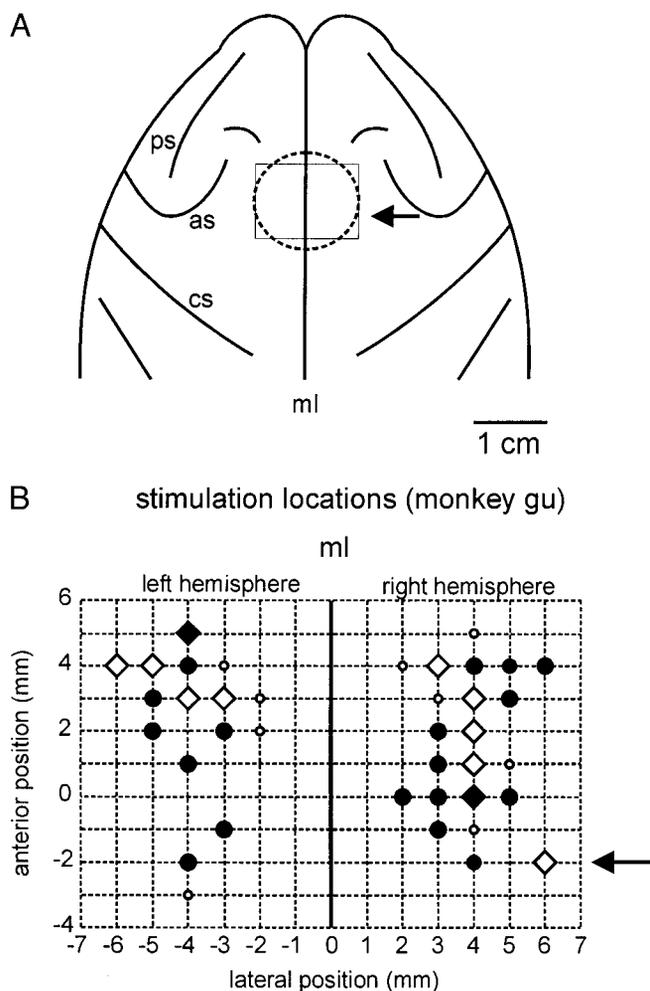


FIG. 12. A: position of the stimulation chamber in *monkey GU*. \leftarrow , the position of the chamber with respect to the caudal edge of the arcuate sulcus. ps, principal sulcus; as, arcuate sulcus; cs, central sulcus; ml, midline. B: stimulations locations in the coordinate system of the stimulation chamber centered on the midline. \leftarrow , the position of the chamber with respect to the caudal edge of the arcuate sulcus. This position coincides with the position indicated in A \leftarrow . \bullet , sites where pursuit facilitation was obtained; \diamond , sites where saccades were evoked; \circ , sites where no oculomotor effect was found; \blacklozenge , sites where pursuit facilitation and saccades were evoked at different depths along the same stimulation track.

ping was attempted. As shown on Fig. 11B, sites separated by 1 mm on the stimulation grid could evoke saccades or facilitate pursuit. These results show that different kinds of eye movements are not represented in distinct subregions but in an interlaced fashion, perhaps indicating the existence of a columnar organization. Since *monkey SA* was still involved in other experiments, the distribution of different sites could not be established in that monkey.

DISCUSSION

This study shows for the first time that electrical stimulation in the dorsomedial frontal cortex, in the region corresponding to the SEF, can induce facilitation of smooth pursuit initiation in the awake behaving monkey. Pursuit facilitation was obtained at sites different from where saccades could be evoked. Stimulation was effective during the time of movement preparation near the end of the fixation period. Catch-up saccades

during pursuit were delayed during pursuit facilitation, but their accuracy was unaffected. The relationship between eye velocity in control and in stimulation trials suggests that the stimulation alters a gain mechanism, i.e., increases the performance of the system, without actually being involved in the direct initiation of the movement as suggested by the absence of effect during a fixation task and on pursuit latency.

Interconnection of the SEF with motion processing and pursuit pathways

The region of the DMFC where stimulation was applied is similar to what was functionally defined as the SEFs in the saccadic domain. Therefore the results of this study suggest that the SEF is part of the smooth pursuit pathway, in addition to their previously shown involvement in the saccade pathway (Schlag and Schlag-Rey 1987). This hypothesis is supported by anatomical studies of the projections of the motion processing pathway to this region of the frontal cortex. Cortical structures involved in motion processing include two regions of the temporal cortex, the middle temporal area (MT) and the medial superior temporal area (MST). Lesions of these areas impair motion processing and smooth pursuit (Dursteler and Wurtz 1988; Newsome et al. 1985). MT and MST are sensory areas, but area MST also contains neurons whose activity can be correlated with the movement of the eye during pursuit (Newsome et al. 1988). Area MST and the neighboring region of the fundus of the superior temporal sulcus project to the region of the FEF and to a region dorsomedial to the upper arcuate limb of the arcuate sulcus (Huerta and Kaas 1990; Maoili et al. 1998). This latter region corresponds to the DMFC and probably also with the SEF. This projection of the motion processing and pursuit pathways to the region of the SEF supports recent results of recordings in that area during pursuit. Heinen (1995) and Heinen and Liu (1997) have shown that some neurons in that area are active during smooth pursuit. In the Telazol-anesthetized monkey preparation, electrical stimulation in the SEF yields either saccades or smooth pursuit (Tian and Lynch 1995). In human subjects, activation of a region of the DMFC corresponding probably with the SEF during smooth pursuit has also been described using imaging techniques (Berman et al. 1999; O'Driscoll et al. 2000; Petit and Haxby 1999; Petit et al. 1997). The connectivity between FEF and SEF suggests that the smooth pursuit region of the FEF area could also project to the SEF (Tian and Lynch 1996b). Altogether, these results support the hypothesis that the SEF is part of the smooth pursuit pathway. Moreover, the SEF projects to the nucleus reticularis tegmenti pontis (NRTP) (Shook et al. 1990), which is known to be an important relay in the subcortical pathway for pursuit (Suzuki et al. 1999; Yamada et al. 1996).

Comparison with other studies of electrical stimulation in the motion/pursuit pathway

Komatsu and Wurtz (1989) showed that electrical stimulation in the foveal representation of MT and MST alters smooth pursuit. These authors found an increase of smooth pursuit velocity toward the side of the brain being stimulated. The most prominent effect, however, was a decrease in pursuit velocity in the contraversive direction. Stimulation was more

effective during pursuit than during fixation and catch-up saccades as well as saccades toward stationary targets were significantly delayed during stimulation in the MT-MST complex. Komatsu and Wurtz (1989) interpreted these results by suggesting that stimulation introduced an additional motion signal in the motion processing pathway. This interpretation was supported by a recent study of electrical microstimulation in area MT (Groh et al. 1997). These authors showed that electrical stimulation in area MT introduces an artificial motion signal that increases the velocity of the eye in the preferred direction and decreases eye velocity in the null direction. Electrical stimulation in a later stage of the pursuit system has produced a different type of results. Stimulation in the FEF pursuit area evokes smooth eye movements during fixation (Gottlieb et al. 1993; Tian and Lynch 1996a). These authors suggested that the stimulation triggers an eye acceleration signal. Recently, Tanaka and Lisberger (2001) showed that stimulation in the FEF pursuit area increases strongly eye velocity during pursuit and moderately during fixation. Moreover, stimulation enhances the response to a transient perturbation of target motion during fixation. The authors suggest that the FEF sets the gain for smooth pursuit and could be involved in the process of target selection.

In our study, pursuit facilitation does not appear to result from the introduction of an additional directional target motion signal as occurs when stimulating in the motion processing pathway (Groh et al. 1997). First, introducing a directional signal should increase eye velocity in one direction and decrease it in the opposite direction. The bilateral or omnidirectional effects which we often observed are not reconcilable with the hypothesis of the addition of a directional motion input. Second, the finding that sustained pursuit was not altered by stimulation suggests that stimulation did not simply add a certain signal in the motion processing pathway during an ongoing smooth eye movement. Neither did stimulation evoke an additional eye velocity command that would be combined with the ongoing movement. Addition of an eye velocity command would always increase eye velocity by a constant amount, probably depending on the stimulation parameters and on the particular site being stimulated. We suggest that our results can be explained better by an alteration of a gain mechanism in the premotor pathway for pursuit by electrical stimulation. This results in a multiplication of eye velocity in controls by a certain amount (in this case, ~ 1.2). In the relationship between target and eye velocity in controls and stimulation trials (see Fig. 7B), the saturation reflects limits of the motion processing pathway in transforming a retinal slip signal into an eye acceleration command (Lisberger and Westbrook 1985; Lisberger et al. 1981). Compared with the results of Tanaka and Lisberger (2001) obtained in the FEF, our results extend the possibility of a gain control of smooth pursuit to the SEF. Both areas are interconnected (Stanton et al. 1993), raising the question of their relative involvement in this process.

Interaction between different kinds of eye movements

The results of this study suggest a causal relationship between facilitation of pursuit and delay of the catch-up saccade, i.e., the catch-up saccade was delayed *because* smooth pursuit was facilitated, because saccades toward stationary targets

were not affected. In natural circumstances, acquisition of a moving target requires a combination of saccades and smooth pursuit. A behavioral study has shown that the latency of the catch-up saccade increases if eye acceleration is larger for a target moving at the same velocity (Kim et al. 1998). Therefore electrical stimulation, by artificially increasing eye acceleration and velocity, might delay the catch-up saccade by a similar mechanism. Interfering with the initial smooth eye acceleration alters the timing of the next movement in the sequence, the catch-up saccade. It has been shown that lesions of the DMFC affects sequences of saccades more than single movements (Schiller and Chou 1998; Sommer and Tehovnik 1999). Therefore that part of the cortex might be activated when sequences of eye movements are planned. Initiation of smooth pursuit can also be considered as a sequence of two different movements: an initial smooth eye acceleration and a subsequent catch-up saccade. Although this hypothesis needs further investigation, it could be suggested that the region of the SEF might contain modules, perhaps columns, active during different kind of eye movements. Interactions between nearby modules could be the neuronal basis of the functional interaction between oculomotor systems.

Task dependency

An obvious difference between this study and the work of Tanaka and Lisberger (2001) is the absence of effect of microstimulation in the SEF during fixation. Smooth movements can be evoked from the FEF pursuit area during fixation, possibly because it is directly connected to the final pathway for pursuit eye movements, which may not be the case for the SEF. Alternatively, the activity of neurons in the SEF could be "gated" by fixation signals. Therefore the facilitation effect in the SEF could be considered as task dependent. In the authors' experience, smooth eye movements are usually more difficult to evoke electrically from a pursuit area than saccades from a saccadic area. This might be the consequence of the different modes of control of these eye movements. Indeed, primates can trigger saccades in the absence of an external stimulus. Smooth pursuit eye movements cannot be initiated voluntarily under normal conditions but needs the presence of a visual motion signal or an expectation about future target motion.

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