Suppression of smooth pursuit eye movements induced by electrical stimulation of the monkey frontal eye field

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Izawa Y, Suzuki H, Shinoda Y. Suppression of smooth pursuit eye movements induced by electrical stimulation of the monkey frontal eye field. J Neurophysiol 106: 2675–2687, 2011. First published August 17, 2011; doi:10.1152/jn.00182.2011.—This study was performed to characterize the properties of the suppression of smooth pursuit eye movement induced by electrical stimulation of the frontal eye field (FEF) in trained monkeys. At the stimulation sites tested, we first determined the threshold for generating electrically evoked saccades (Esacs). We then examined the suppressive effects of stimulation on smooth pursuit at intensities that were below the threshold for eliciting Esacs. We observed that FEF stimulation induced a clear deceleration of pursuit at pursuit initiation and also during the maintenance of pursuit at subthreshold intensities. The suppression of pursuit occurred even in the absence of catch-up saccades during pursuit, indicating that suppression influenced pursuit per se. We mapped the FEF area that was associated with the suppressive effect of stimulation on pursuit. In a wide area in the FEF, suppressive effects were observed for ipsiversive, but not contraversive, pursuit. In contrast, we observed the bilateral suppression of both ipsiversive and contraversive pursuit in a localized area in the FEF. This area coincided with the area in which we have previously shown that stimulation suppressed the generation of saccades in bilateral directions and also where fixation neurons that discharged during fixation were concentrated. On the basis of these results, we compared the FEF suppression of pursuit with that of saccades with regard to several physiological properties and then discussed the role of the FEF in the suppression of both pursuit and saccades, and particularly in the maintenance of visual fixation.

THE FRONTAL EYE FIELD (FEF) plays a prominent role in saccade generation. Electrical stimulation of the FEF elicits saccades at low intensities (Bruce et al. 1985; Robinson and Fuchs 1969), and the FEF contains neurons with visual activity and neurons with presaccadic burst activity (Bruce and Goldberg 1985). In addition, the FEF has been shown to contribute to the generation of smooth pursuit eye movements (Bruce et al. 1985; Ebata et al. 2004; MacAvoy et al. 1991; Tanaka and Fukushima 1998; Tian and Lynch 1996). The smooth pursuit subregion of the FEF is known to be a discrete region that is near the spur of the arcuate sulcus and has been reported to play a role in the initiation and maintenance of smooth pursuit (Ono and Mustari 2009; Tanaka and Lisberger 2002a). The pathways for pursuit that originate in the FEF constitute a parallel system with the traditional cortico-ponto-cerebellar pathways for pursuit that originate in the middle temporal area (MT) and medial superior temporal area (MST) (see reviews: Keller and Heinen 1991; Lisberger et al. 1987). Recent studies have suggested that the pursuit pathways through the FEF include premotor brain stem structures shared with the saccadic system (see review in Krauzlis 2004).

Although the FEF has been implicated in the generation of eye movements, the FEF also exerts suppressive control on eye movements. Stimulation of the FEF has been shown to suppress the generation of saccades at stimulus intensities that were lower than those for eliciting electrically evoked saccades (Esacs) (Azuma et al. 1986; Burman and Bruce 1997; Izawa et al. 2004a, 2004b). Stimulation in a wide area of the FEF suppressed only ipsiversive visually guided (Vsacs) and memory-guided saccades (Msacs) (Izawa et al. 2004a), whereas stimulation of a localized area of the FEF in the caudal part of the arcuate gyrus facing the inferior arcuate sulcus suppressed both Vsacs and Msacs in any direction (Izawa et al. 2004b). Functionally, the suppression of eye movements is essential during visual fixation to hold the image of the target on the fovea. Appropriate eye movements should be allowed to occur only after their suppression by the fixation system is released. In fact, the FEF also contains fixation neurons that show activity related to visual fixation (Bizzi 1968; Bruce and Goldberg 1985; Suzuki and Azuma 1977), and these fixation neurons have been shown to be concentrated in the bilateral suppression area for saccades (Izawa et al. 2004b, 2009). During fixation, potential eye movements other than saccades should also be suppressed. In the rostral superior colliculus (SC) (Munoz and Guittton 1991; Munoz and Wurtz 1993) and the omnipause neuron (OPN) region (Cohen and Henn 1972; Keller 1974; Luschei and Fuchs 1972; Ohgaki et al. 1987; Strassman et al. 1987), where neurons show continuous activity during fixation, the suppression of smooth pursuit was previously shown by stimulation. Stimulation of the rostral SC suppressed pursuit to ipsiversive moving targets, whereas contraversive pursuit was less affected and was either facilitated or suppressed (Basso et al. 2000). Stimulation of the OPN region induced a deceleration of the eye during smooth pursuit (Missal and Keller 2002). The suppressive effect was exerted on smooth pursuit in both directions but had laterality, although it is difficult to determine the side of the brain stem that is stimulated due to the proximity of the OPN region to the midline. Stimulation of the OPN region has also been shown to suppress vergence movements (Mays and Gamlin 1995).

The present study was performed to investigate the effects of electrical stimulation of the FEF and its vicinity on smooth pursuit in trained monkeys. The results showed that FEF stimulation strongly suppressed both the initiation and maintenance phases of smooth pursuit. We found two types of
suppression for smooth pursuit: ipsilateral and bilateral. The areas associated with the ipsilateral and bilateral suppression for smooth pursuit corresponded to those associated with the ipsilateral and bilateral suppression of saccades (Izawa et al. 2004a, 2004b), respectively. This report describes the characteristic properties of both types of suppression of smooth pursuit caused by stimulation of the FEF and discusses the functional implications of this suppression of pursuit in relation to visual fixation. These results have been briefly reported previously (Izawa et al. 2010).

METHODS

Experiments were performed in two male Japanese monkeys (Macaca fuscata) weighing 7 and 9 kg, respectively. The surgical procedures have been described in previous reports on experiments in which the same monkeys were used (Izawa et al. 2004a, 2004b). All animal experimentation was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, Washington, DC: National Academy Press, 1996) and the “Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences” (The Physiological Society of Japan, revised in 2001). All surgical and experimental protocols were approved by the Animal Care Committee of Tokyo Medical and Dental University.

Behavioral Training

During training and experimental sessions, the monkey was seated in a primate chair facing a tangent translucent screen 1.5 × 1.5-m square and 57 cm in front of it. Each monkey was first trained to fixate on a tiny light spot (0.4° in visual angle, 2 cd/m²) that was back-projected at the center of the screen using a pair of mirrors attached to galvanometers (Suzuki and Azuma 1977; Wurtz 1969). The screen was evenly illuminated at 1 cd/m² to eliminate stray light around the spot. The monkey was trained to press a bar with its hand on the appearance of the center spot, which occurred after an intertrial interval of 5 s. While the bar was held down, the spot remained illuminated for a variable duration of 1–4 s and then was slightly brightened (0.3 log unit) for 0.5 s. If the monkey released the bar during this short brightening period, it received 0.2 ml of juice as a reward. Otherwise, the trial was terminated without a reward, and a new trial began. Fixation behavior was elicited, since the monkey had to look at the spot to notice its brightening for rapid bar release. The monkey was required to maintain its line of sight within an error window of ± 2° around the fixation target.

When the training of the fixation task was completed, the monkey was required to make visually guided saccades (Vsacs) and smooth pursuit. For the Vsac task, the center spot was turned off and another light spot was simultaneously turned on elsewhere on the screen as a visual target. The monkey learned to make a saccade to the target, since it had to observe its brightening. If the monkey released the bar during brightening of the target light, it received a reward. In the smooth pursuit task, the monkey first fixed its eyes on the center spot for 1.5 s. After this fixation period, the target moved at a constant velocity. Usually, the velocity and amplitude of target motion were 15 or 20°/s and 15 or 20°, respectively. At the end of this pursuit period, the target stopped and the monkey was required to fixate on it for 0.5–1.5 s to detect a change in illumination and release the bar for a reward. To observe early pursuit trajectories without catch-up saccades, the target was also given an initial step (2°) in a direction opposite the velocity of the target (step-ramp target motion; Rashbass 1961).

Microstimulation and Experimental Procedures

We used glass-insulated elgiloy microelectrodes (Suzuki and Azuma 1976) with impedances of 0.3–0.5 MΩ at 1 kHz in Ringer solution. The electrode was introduced into the left FEF with a micromanipulator (MO-95; Narishige, Tokyo, Japan) attached to an implanted cylinder that was centered at A25, L18 for one monkey and at A30, L20 for the other monkey. While recording neuronal activity within the cortex, we switched from a recording circuit to a stimulation circuit at cortical depth intervals of 200 or 400 μm to apply microstimulation using the same electrode. Constant-current stimulation trains were generated using a Nihon Kohden ss-1945 stimulator. Trains generally consisted of 40–80 monopolar cathodal pulses of 1-ms duration at 200 Hz and ≤80 μA. During data collection, the monkey first performed a fixation task. In stimulation trials, microstimulation was first applied to the FEF during fixation at the center spot, and the threshold for evoking eye movements was determined. In subsequent stimulation trials, the monkey was instructed to make Vsacs, and the onset of the target spot was usually accompanied by the onset of a train of stimulation pulses. Current intensities were varied systematically to determine the threshold for suppressive effects on Vsacs. For further details regarding the stimulus parameters for eliciting Esacs and suppressing Vsacs, see Izawa et al. (2004a, 2004b). After we identified the suppression sites for Vsacs, we examined the effect of stimulation on smooth pursuit. A train of stimulation pulses was usually applied at the onset of target motion or 200–500 ms after the onset of target motion. Virtually all sites in the following descriptions were judged to be in the gray matter based on the background neuronal activity recorded before stimulation. In each track, the effect of stimulation was systematically examined throughout the gray matter and the white matter beneath the FEF. Several representative stimulation sites in one monkey were marked with iron deposits by passing currents (electrode positive, 400 μA) through the elgiloy microelectrode (Suzuki and Azuma 1987). At the end of the experiment, the monkeys were deeply anesthetized with pentobarbital sodium and perfused with 6 liters of saline followed by 6 liters of a fixative solution containing 10% formalin. For one monkey with marked recording sites, the fixative solution also contained 2% ferrocyanide. Serial frozen sections 80 μm thick were cut coronally from the frontal cortex and stained with thionine. The sections were reconstructed using a camera lucida system. Stimulation and recording sites were histologically verified to be located in the prearcuate gyrus.

Experimental Control and Data Acquisition

The behavioral tasks, presentation of light spots, and data acquisition were controlled by IBM-compatible computers. Eye movements were recorded by a camera measurement system, using the corneal reflection image of infrared light (Azuma et al. 1996), with which we could measure horizontal and vertical eye positions with an accuracy of 0.3° and at a sampling rate of 4 ms. Eye position signals were calibrated by having the monkey fixate on targets at known eccentricities (10, 20, and 30°) on the horizontal and vertical meridians and diagonal axes. Horizontal and vertical component signals of eye movements and neuronal activity with respect to behavioral event indicators were stored on computer hard disks and displayed on an oscilloscope. Eye movements and neuronal activity were sampled every 4 and 1 ms, respectively. The onset of each saccade was identified in the eye position traces by a mouse-controlled cursor. Subsequent off-line data analyses were performed using Matlab (MathWorks, Natick, MA) programs. Mean eye position traces were obtained by aligning the data with respect to the onset of target motion and calculating the mean within each 4 ms of the data. To obtain eye velocity, the mean eye position signal was digitally differentiated. Eye velocity was low-pass filtered with a moving average of five data points (–6 dB, 30 Hz). We measured the mean eye velocity during a 100-ms period before the end of stimulation for analysis unless stated otherwise. A preferred direction for suppression was given by a value in the fitted Gaussian function. Statistical analysis was performed with
the Mann-Whitney *U*-test and Friedman analysis of variance (ANOVA).

**RESULTS**

**Ipsilateral Suppression of Smooth Pursuit by FEF Stimulation**

We examined the effects of microstimulation of the FEF and its vicinity in the prearcuate gyrus on smooth pursuit. In each track, we first examined depth thresholds for eliciting Esacs and suppressing Vsacs by stimulation (Izawa et al. 2004a, 2004b). This large database of depth-threshold curves for Esacs and the suppression of saccades was used to delineate the FEF in these monkeys physiologically. Figure 1A shows an example of the suppressive effect of FEF stimulation on Vsacs at an intensity (30 μA) that is subthreshold for evoking Esacs (Esac threshold, 45 μA). A stimulus train was applied at the onset of the visual target for Vsacs. This FEF stimulation delayed the generation of Vsacs ipsiversive to the stimulated side (Fig. 1A, ipsi). On the other hand, the same stimulation did not influence contraversive Vsacs (Fig. 1A, contra). After we verified that stimulation had a suppressive effect on ipsiversive Vsacs, we examined the effects of stimulation at the same site on smooth pursuit. In the example in Fig. 1Ba, we applied a stimulus train at an intensity of 30 μA at the onset of target motion at 20°/s. This FEF stimulation delayed the initiation of smooth pursuit ipsiversive to the stimulated side (Fig. 1Ba, ipsi). The suppression of pursuit continued during stimulation, and a saccade occurred to catch up with the target when the stimulation was turned off. These saccades (median 7.0°) were larger than the regular catch-up saccades during the initiation of smooth pursuit in the control (median 2.7°) (*U*-test, *P* < 0.01). In contrast, the same stimulation did not suppress contraversive smooth pursuit (Fig. 1Ba, contra). As in this example, every set of 5–10 stimulation trials was preceded by a set of control (no stimulation) trials. Another set of control trials often followed the stimulation trials to ensure that the effect was not due to a temporal factor, such as changes in the monkey’s behavior or damage to brain tissue caused by the passage of current. We further obtained the mean eye position and eye velocity to evaluate the suppressive effects of FEF stimulation on pursuit. The mean eye position traces in Fig. 1Bb clearly show the ipsilateral suppression of smooth pursuit. When eye velocity was measured for the mean eye position signal, eye velocity during pursuit initiation included a transient increase that corresponded to catch-up saccades and was followed by eye velocity during maintained pursuit in the control (Fig. 1Bc, 0 μA). During maintained pursuit, eye velocity showed substantial oscillations around the desired velocity (Lisberger et al. 1987). When stimulation was applied, the ipsiversive pursuit velocity did not increase compared with that in the control (Fig. 1Bc, ipsi). After stimulation, eye velocity showed a vigorous increase corresponding to large catch-up saccades. On the other hand, the contraversive pursuit velocity during stimulation was not different from that in the control (Fig. 1Bc, contra).

It is possible that the suppressive effects of FEF stimulation on smooth pursuit were caused by the suppression of small catch-up saccades during smooth pursuit. To examine the effects of FEF stimulation on smooth pursuit without initial catch-up saccades during the onset of pursuit, the target was given an initial step (2°) in a direction opposite the velocity (Fig. 1) and stimulation was applied simultaneously at the onset of the target step. In the control, smooth eye movements started without catch-up saccades during pursuit initiation in both ipsilateral and contralateral directions (Fig. 2Aa, control), as was also indicated by the eye velocity traces (Fig. 2Ab, control). Despite the absence of catch-up saccades, stimulation of the FEF strongly suppressed the initiation of ipsiversive smooth pursuit (Fig. 2Aa, 0 ms). In contrast, the same stimulation did not influence contraversive smooth pursuit without initial catch-up saccades. The ipsilateral suppression of smooth pursuit was also indicated by a deceleration of only ipsiversive smooth pursuit during stimulation in the eye velocity traces (Fig. 2Ab, 0 ms). The mean eye velocity showed a clear decrease during stimulation for ipsiversive smooth pursuit (Fig. 2B, ipsi) but not contraversive pursuit compared with that in the control (Fig. 2B, contra). Therefore, this result indicated that stimulation of the FEF suppressed ipsiversive smooth pursuit per se rather than the initial catch-up saccades. To confirm the suppressive effect of FEF stimulation on smooth
pursuit, stimulation was delivered during maintained pursuit (300 ms after the onset of target motion) (Fig. 2Aa, 300 ms). Despite the difference in the timing of stimulation, a strong deceleration of ipsiversive smooth pursuit occurred while contraversive smooth pursuit remained unchanged (Fig. 2Ab, 300 ms), as was also indicated by the mean eye velocity (Fig. 2B). We did not observe differences between the suppressive effects of stimulation at 0 and 300 ms after the onset of target motion on smooth pursuit. The unilateral suppression of ipsiversive smooth pursuit was found in 41 of 46 tracks in which electrical stimulation at 0 and 300 ms, respectively. Horizontal dotted lines, 0°/s. Vertical dotted lines indicate target motion onset. B: eye velocity (mean ± SE) during a 100-ms period before the end of stimulation at 0 and 300 ms from the onset of target motion in A. Eye velocity (mean ± SE) in the control was measured during a 400-ms period ranging from the period measured in 0-ms-delay stimulation trials to the period measured in 300-ms-delay stimulation trials.

To find the most effective stimulus parameters for the suppression of smooth pursuit, we systematically examined the effects of varying stimulus parameters on the suppression of smooth pursuit. A target moved at 20°/s, and stimulus intensities were increased from 0 to 36 μA at 6-μA intervals (Fig. 3A). Although no clear effect appeared at up to 18 μA, a decrease in eye velocity during ipsiversive smooth pursuit occurred at 24 μA (Fig. 3A, left). When the stimulus intensity was increased to 30 and 36 μA, smooth pursuit was strongly suppressed during stimulation, and a large saccade occurred to catch up with the target ~30 ms after stimulation offset. We measured the mean eye velocity during the 100-ms period after the beginning of stimulation and before the end of stimulation in 0- and 36-μA stimulation trials. Although no effect appeared during the early stimulation period (Fig. 3B, ipsi early), a clear decrease in eye velocity occurred during the late stimulation period as the stimulus intensity increased (Fig. 3B, ipsi late). The threshold for suppression was defined as the lowest stimulus current required to produce a decrease in the mean eye velocity during the 100-ms period before the end of stimulation that was >2 SEs of the mean eye velocity in the control (0 μA). In the example in Fig. 3A, the mean velocity (±SE) in the control condition for ipsiversive pursuit was 19.7 ± 1.7°/s (n = 7). Based on the criterion, we determined that the threshold for suppression in this example was 24 μA. At the same stimulation site, however, contraversive smooth pursuit was not suppressed even at 36 μA (Fig. 3A, right). As

![Figure 2](image1.png)

**Fig. 2.** Suppression of pursuit initiation and pursuit maintenance by FEF stimulation. A: effects of FEF stimulation on ipsiversive and contraversive horizontal smooth pursuit without catch-up saccades during the initiation of smooth pursuit (15° in amplitude). The target was given an initial step (2°) in a direction opposite the velocity (15°/s). a: each trace shows the mean eye position in the control and during stimulation. Top: target position. Stimulation (horizontal bars; 30 μA, 80 pulses) was applied at the onset of target motion (0 ms) and at 300 ms after the onset of target motion (indicated at left). b: each eye velocity profile was obtained from the mean eye position signal in the control and during stimulation shown in a, respectively. Horizontal dotted lines, 0°/s. Vertical dotted lines indicate target motion onset. B: eye velocity (mean ± SE) during a 100-ms period before the end of stimulation at 0 and 300 ms from the onset of target motion in A. Eye velocity (mean ± SE) in the control was measured during a 400-ms period ranging from the period measured in 0-ms-delay stimulation trials to the period measured in 300-ms-delay stimulation trials.

![Figure 3](image2.png)

**Fig. 3.** Effects of stimulus parameters on the suppression of smooth pursuit. A: effects of varying the stimulus intensity on smooth pursuit. Stimulation (60 pulses) was applied with an increasing stimulus intensity (indicated at left) at 300 ms after the onset of target motion for ipsiversive (left) and contraversive (right) horizontal smooth pursuit (20°/s in velocity, 15° in amplitude). The threshold for contraversive electrically evoked saccades (Esacs) at this stimulation site was 40 μA. The bottom trace in each column shows a behavioral event indicator. The first and second upward steps indicate the onset of target motion and stimulation, respectively. The downward step indicates the cessation of stimulation, but with the target light on. B: eye velocity (mean ± SE) during the 100-ms periods after the beginning of stimulation (ipsi early, contra early) and before the end of stimulation (ipsi late, contra late) in stimulation trials shown in A. C: effects of varying the number of stimuli on the suppression of ipsiversive horizontal smooth pursuit (20°/s in velocity, 15° in amplitude). Zero to 120 pulses of stimuli at 200 Hz (horizontal bars; stimulus intensity, 30 μA) were applied at 200 ms after the onset of target motion (vertical dotted lines). Each trace in A and C shows the mean eye position. Dotted trace indicates target position.
with ipsiversive pursuit, we measured the mean eye velocity for contraversive pursuit during the 100-ms periods after the beginning of stimulation (Fig. 3B, contra early) and before the end of stimulation (Fig. 3B, contra late). At either stimulus intensity, the mean eye velocity did not differ from that in the control by 2 SEs during both the early and late stimulation periods, indicating that no effect appeared for contraversive smooth pursuit. The thresholds for the suppression of ipsiversive smooth pursuit were almost the same as or slightly lower than those of ipsiversive Vsacs at all 18 stimulation sites tested.

Figure 3C shows an example of the effect of varying the train duration on ipsiversive pursuit suppression. The train duration was increased by changing the number of pulses in a stimulus train while the stimulus intensity and interval were kept constant. In this example, a stimulus intensity of 30 μA for 200 ms (40 pulses), which was well below the threshold for evoking Esacs (50 μA), was strong enough to suppress the generation of smooth pursuit. A train of 80 stimulus pulses clearly decreased pursuit velocity. Smooth pursuit was further strongly suppressed during stimulation for up to 600 ms (120 pulses). As in this case, stimulation at a sufficiently suprathreshold intensity generally caused the suppression of smooth pursuit during stimulation. Similar results were obtained at all eight ipsilateral suppression sites tested. However, suppression did not always continue during stimulation, but rather depended on the stimulation site and intensity, so catch-up saccades and subsequent smooth pursuit in some trials occurred even during prolonged stimulation.

Suppressive effects of ipsilateral suppression sites on smooth pursuit in different directions. To determine the effective direction of suppression, we changed the direction that the target moved among eight cardinal directions with the pursuit amplitude (15°) and velocity (20°/s) fixed (Fig. 4) and examined the suppressive effects of FEF stimulation on smooth pursuit. The velocity of smooth pursuit for these eight directions was significantly decreased in stimulation trials compared with that in control trials (Friedman ANOVA, P < 0.001). Suppression occurred predominantly for smooth pursuit with an ipsilateral horizontal component (Fig. 4A, a–c) and slightly for purely vertical smooth pursuit with an upward (Fig. 4Ad) or downward direction (Fig. 4Ah). The mean eye velocity showed a clear decrease during stimulation >2 SEs of that in the control for 135, 180, and 225° (Fig. 4B, a–c). In contrast, suppression was not observed for smooth pursuit with a contralateral horizontal component (Fig. 4B, e–g). During oblique smooth pursuit, the horizontal and vertical components were synchronously suppressed by stimulation. After the suppression of oblique pursuit, we sometimes observed that the monkey tended to make catch-up saccades with a larger horizontal component than vertical component, which corrected the horizontal component before the vertical component (compare the bottom pair of traces in Fig. 4Ac). The preferred direction for the suppression of smooth pursuit was determined by using the difference in eye velocity between smooth pursuit in stimulation and control trials as an index of the strength of the suppression in each direction, since the smooth pursuit velocities in different directions were varied in the control. In the example in Fig. 4, suppression showed a preference for the ipsilateral downward direction (185.3°). To examine the relationship between the directions of Esacs and suppression, we increased the stimulus intensity at the same stimulation site and evoked Esacs. Esacs were evoked at a threshold of 50 μA to the contralateral upward direction (32.8°) (Fig. 4B, arrow). We compared the preferred direction of suppression and the Esac direction at all 4 stimulation sites where similar unilateral suppression was observed. The preferred direction of suppression was in the quadrant diagonally opposite the quadrant for the direction of Esacs at three stimulation sites, whereas at the remaining site, the directions of suppression and Esacs were in the quadrants where the vertical components were the same and the horizontal components were opposite.

Fig. 4. Suppressive effects of FEF stimulation on smooth pursuit with different directions. A: smooth pursuit of a target moving at 20°/s in 8 directions (15° in amplitude) in the control and during FEF stimulation. a–h correspond to target directions of 135, 180, 225, 270, 315, 0, 45, and 90°, respectively. By convention, right horizontal movement has a direction of 0°, up = 90°, left = 180°, and down = 270°. The top and bottom pairs of traces in individual records (a–h) indicate horizontal and vertical components of the mean eye position in the control and during stimulation (40 μA, 60 pulses, 300 ms after target motion onset), respectively. Dotted trace indicates target position. The threshold for Esacs at this stimulation site was 50 μA. The bottom trace in each column shows a behavioral event indicator in the same manner as in Fig. 3A. B: polar representation of the mean velocity of smooth pursuit in the control (thin line) and FEF stimulation trials (thick line) shown in A. a–h correspond to those in A. Arrow indicates direction of Esacs. U, up; D, down.
Suppressive effects of FEF stimulation on smooth pursuit with different velocities. To investigate the suppressive effects of FEF stimulation on smooth pursuit in terms of target velocities, we changed the velocity of the target for pursuit at eight stimulation sites. In the example in Fig. 5, the target moved at 0, 10, 20, 40, 100, and 1,000°/s. Pursuit of targets moving at 0 and 1,000°/s corresponded to fixation and saccade, respectively. The intermediate target velocities were set to examine the transition from smooth pursuit to saccades. Under the control condition with no stimulus, the smooth pursuit velocity increased as the target velocity increased (Fig. 5A, left). When the stimuli were applied at the onset of target motion at 21 μA, slight suppression was seen for the initiation of ipsiversive smooth pursuit with velocities of 10–100°/s and ipsiversive Vsacs (Fig. 5A, middle). On the other hand, the same stimulation did not suppress contraversive smooth pursuit at any velocity or Vsacs. At 35 μA, all ipsiversive smooth pursuit movements with velocities of 10–100°/s and Vsacs were suppressed (Fig. 5A, right). The suppressive effects on smooth pursuit did not clearly depend on the target velocity. Initial catch-up saccades occurred relatively later in smooth pursuit after the suppression of pursuit with lower velocity. In this example, when the stimulus intensity was increased (e.g., 35 μA), catch-up saccades occurred with very different timings in each record, resulting in a train of small saccades in the mean eye position. Again, contraversive smooth pursuit and Vsacs were not suppressed at all by the same stimulation. In addition to the effects of stimulation during the initiation of smooth pursuit, the effects of stimulation during maintained pursuit with different velocities were examined. As shown in Fig. 5B, stimulation during maintained pursuit also suppressed ipsiversive smooth pursuit with different velocities from 20 to 80°/s at intervals of 20°/s. Therefore, this result indicated that both the initiation of smooth pursuit and maintained pursuit with different velocities were suppressed by stimulation of the FEF.

Bilateral Suppression of Smooth Pursuit by FEF Stimulation

When we systematically examined the effects of stimulation of the FEF and its vicinity in the prearcuate gyrus on saccades, we found that a localized area in one FEF suppressed Vsacs in both the ipsilateral and contralateral directions (Izawa et al. 2004b). In this area of bilateral suppression, we examined the effects of stimulation on smooth pursuit in either direction. A typical example of stimulation at such a site is shown in Fig. 6. Stimulation at 24 μA completely suppressed the generation of both ipsiversive and contraversive Vsacs during stimulation (Fig. 6A). To examine the effects of stimulation at the same site on smooth pursuit, stimulation with the same stimulus parameters was applied during maintained pursuit (Fig. 6B). We found that stimulation suppressed the generation of ipsiversive smooth pursuit (Fig. 6Ba, ipsi). This suppression of ipsiversive smooth pursuit is very similar to the unilateral suppression of smooth pursuit described in the preceding section. In addition, the same stimulation also suppressed the generation of contraversive smooth pursuit (Fig. 6Ba, contra). The bilateral suppression of smooth pursuit was also indicated by the deceleration of both ipsiversive and contraversive smooth pursuit during stimulation in the eye velocity traces (Fig. 6Bb). Therefore, stimulation at this site suppressed smooth pursuit as well as Vsacs in both directions. To exclude the possibility that the suppressive effects of FEF stimulation on smooth pursuit in both directions were caused by the suppression of small catch-up saccades during pursuit, we also examined the effects of FEF stimulation on smooth pursuit without initial catch-up saccades (Fig. 6C). The target was given an initial step (2°) in a direction opposite the velocity so that the initiation of smooth pursuit was not accompanied by catch-up saccades in either direction in the control. When stimulation was applied at the onset of the target step, the initiation of both ipsiversive (Fig. 6Ca) and contraversive smooth pursuit was suppressed during stimulation despite the absence of catch-up saccades (Fig. 6Cc). A deceleration of smooth pursuit in both directions was also indicated by the eye velocity traces during stimulation (Fig. 6Cc, a and d). The mean eye velocity of ipsiversive smooth pursuit showed a clear decrease during stimulation >2 SEs of that in the control (Fig. 6Dd, ipsi). As with ipsiversive pursuit, the mean eye velocity clearly decreased during stimulation for contraversive smooth pursuit >2 SEs of that in the control (Fig. 6Dc, contra). Therefore, these results indicated that stimulation of the FEF suppressed smooth pursuit per se bilaterally. In contrast to saccades in which their initiation was
suppressed completely (Fig. 6A), smooth pursuit without catch-up saccades tended to be merely slowed by stimulation at bilateral suppression sites in the FEF (Fig. 6C). This tendency was also observed at ipsilateral suppression sites in the FEF (Fig. 2A). Of the 72 tracks examined, 30 had bilateral suppression sites for Vsacs, and 22 of these had sites at which smooth pursuit at the same site as in A. The velocity and amplitude of target motion were 20°/s and 15°, respectively. Vertical dotted lines show the mean eye position in control and stimulation trials, respectively. Stimulation (24 μA, 60 pulses) was applied at 300 ms after the onset of target motion. Amplitude calibration in A also applies to Ba. a: top and bottom eye velocity profiles were obtained from the mean eye position signal in the control and during stimulation shown in a, respectively. Horizontal dotted lines, 0°/s. Vertical dotted lines indicate target motion onset. C: effects of FEF stimulation on ipsiversive and contraversive horizontal smooth pursuit without catch-up saccades during the initiation of smooth pursuit (15°/s in velocity, 15° in amplitude). The target was given an initial step (2°) in a direction opposite the velocity so that catch-up saccades did not occur during the 100-ms period before the beginning of stimulation (ipsi early, contra early) and before the end of stimulation (ipsi late, contra late) in stimulation trials shown in A and C, respectively. Horizontal dotted lines, 0°/s. D: eye velocity (mean ± SE) during the 100-ms periods after the beginning of stimulation at 0 and 15 μA in C.

Stimulus parameters for effective bilateral suppression of smooth pursuit. Using the same procedure that we used to examine the effects of suppression on ipsiversive smooth pursuit, we examined the effects of varying the stimulus intensity (Fig. 7, A and B) and the number of stimulus pulses (Fig. 7C) on the suppression of smooth pursuit in both directions. When stimulus intensities were increased from 0 to 30 μA at 6-μA intervals, stimulation at 6 and 12 μA had no effect on smooth pursuit (Fig. 7A, left). However, FEF stimulation at 18 μA slightly decreased eye velocity during ipsiversive smooth pursuit. With stimulus intensities of 24 and 30 μA, the generation of ipsiversive pursuit was more strongly suppressed, and a large saccade occurred to catch up with the target ~50 ms after stimulation offset. We measured the mean eye velocity during the 100-ms period after the beginning of stimulation and before the end of stimulation in 0–30 μA stimulation trials. Although no effect appeared during the early stimulation period (Fig. 7B, ipsi early), a clear decrease in eye velocity occurred during the late stimulation period as the stimulus intensity was increased (Fig. 7B, ipsi late). At the...
same stimulation site, contraversive smooth pursuit was also
suppressed in some trials at 18 μA (Fig. 7A, right). With
stimulus intensities of 24 and 30 μA, the suppression of
contraversive smooth pursuit became stronger and persisted for
up to ~120 ms after the offset of stimulation, and a saccade
then occurred to catch up with the target. This saccade was
larger than the regular catch-up saccades during smooth pur-
suit. We measured the mean eye velocity for contraversive
pursuit during the same 100-ms periods as for ipsiversive
pursuit. As with ipsiversive pursuit, there was no clear decrease
in eye velocity during the early stimulation period (Fig. 7B,
contra early). However, a clear decrease in eye velocity oc-
curred during the late stimulation period as the stimulus inten-
sity was increased (Fig. 7B, contra late). Based on the criterion
in the preceding section, we determined that the threshold for
the suppression of both ipsiversive and contraversive smooth
pursuit was 18 μA in the example in Fig. 7A. The thresholds
for the bilateral suppression of smooth pursuit were almost the
same as or slightly lower than those of Vsacs at all 15
stimulation sites tested.

The effects of varying the number of stimulus pulses were
examined with a stimulus intensity fixed at a suprathreshold
value of 15 μA (Fig. 7C). An increase in the number of
stimulus pulses similarly increased the duration of suppression of
ipsiversive and contraversive smooth pursuit. Similar results
were obtained at all five bilateral suppression sites examined.
However, the suppression of smooth pursuit did not always
persist throughout the entire duration of a prolonged stimulus
train. This tendency was also observed in some trials with the
stimulation of unilateral suppression sites.

Suppressive effects of bilateral suppression sites on smooth
pursuit with different directions. To determine the effective
direction of suppression, we examined the suppressive effects of
FEF stimulation on smooth pursuit by changing the direction
of pursuit to one of eight cardinal directions with the amplitude
(15°) and velocity (20°/s) kept constant. Both ipsiversive
(Fig. 8A, a–c) and contraversive smooth pursuit (Fig. 8A, e–g)
in any direction was strongly suppressed in all trials. Purely
vertical upward (Fig. 8Ah) and downward smooth pursuit (Fig.
8Ad) was also sufficiently suppressed by the same stimulation.
The decrease in pursuit velocity in eight directions indicated
that stimulation of this FEF site significantly suppressed
smooth pursuit (Friedman ANOVA, $P < 0.0001$) (Fig. 8B).

The mean eye velocity showed a clear decrease during stimu-
lation >2 SEs of that in the control in all eight directions.
Similar results were obtained at all six bilateral suppression
sites examined. Stimulation of bilateral suppression sites de-
layed both the horizontal and vertical components of individual
oblique smooth pursuit (Fig. 8A). After the suppression of
oblique pursuit, we sometimes observed that the monkey made
catch-up saccades with different amplitudes in the horizontal
and vertical components. As in the unilateral suppression of
oblique pursuit, these catch-up saccades tended to have a larger
horizontal component than vertical component to correct the
horizontal component before the vertical component (compare the
bottom pair of traces in Fig. 8Ac).

Relationship between pursuit suppression and saccade
generation. It is possible that stimulation of a bilateral
suppression site evokes unnoticeable Esacs that fix the eyes on
the position. To test this supposition, we tried to make such
minimal Esacs overt by changing the initial eye position. The
amplitude of Esacs during fixation increases as the initial eye
position shifts toward the direction opposite the Esacs, even
when they are evoked by stimulation with identical stimulus
parameters (Izawa et al. 2004b). Therefore, unnoticeable Esacs
should become noticeable by changing the initial eye position
to the direction opposite the Esacs (ipsilateral to the stimulated
side). We shifted the initial starting eye position of smooth
pursuit from contralateral 20° to ipsilateral 10° at intervals of
5 or 10°. Figure 9A shows an example of the effect of changing
the initial eye position on the amplitude of contraversive Esacs
during ipsiversive pursuit of a target moving at 10°/s. Stimu-

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**Fig. 8.** Bilateral suppression of smooth pursuit in differ-
ent directions. A: smooth pursuit of a target moving at
20°/s in 8 directions (15° in amplitude) in the control and
during FEF stimulation (30 μA, 40 pulses, 300 ms after
target motion onset; a–b). Arrangement is the same as in
Fig. 4. At this stimulation site, Esacs were not evoked
even at 80 μA. Vertical dotted lines indicate target
motion onset. B: polar representation of the mean velo-
city of smooth pursuit in control (thin line) and stimula-
tion trials (thick line) shown in A.
Stimulation of a FEF site produced 14.9° Esacs during pursuit from an initial eye position of contralateral 20° (Fig. 9A, contra 20°). As the initial eye position was shifted toward the direction opposite the Esacs, the amplitude of Esacs gradually increased and became 21.8° during pursuit from an initial eye position of ipsilateral 10° (Fig. 9A, ipsi 10°). As in this example, the amplitude of Esacs during smooth pursuit greatly increased as the initial eye position changed toward the direction opposite the Esacs. Taking advantage of this property, we examined the possibility that stimulation of a bilateral suppression site might produce tiny Esacs with an amplitude of <0.3°, which was below the sensitivity of our eye-measuring system. Stimulation of a bilateral suppression site suppressed smooth pursuit bilaterally but did not evoke any identifiable Esacs during pursuit from an initial eye position of contralateral 20° at 20 μA. Even though the initial eye position was shifted in the ipsilateral direction, contraversive Esacs could not be identified with our recording system (Fig. 9B). This result supports the interpretation that the suppression of smooth pursuit cannot be attributed to tiny contraversive Esacs. Similar results were obtained at the eight stimulation sites tested.

**Depth thresholds for the suppression of smooth pursuit.** To understand the relationship between the suppression sites for smooth pursuit and saccades, we always examined the effect of stimulation on smooth pursuit after we identified suppression sites for Vsacs. Figure 10A shows an example of the depth thresholds for eliciting Esacs and suppressing Vsacs and smooth pursuit at the cortical site indicated by an arrow in Fig. 10B. At the superficial depths in this track, the thresholds for Esacs decreased with advancement of the electrode and reached 20–15 μA at a depth of 2,400–3,200 μm. Only ipsiversive Vsacs were suppressed at stimulus intensities lower than those that elicited Esacs at a depth of 1,200–2,000 μm. In this ipsilateral suppression area for saccades, we examined the suppressive effect of stimulation on smooth pursuit at a depth of 1,600 μm. Again, only ipsiversive smooth pursuit was suppressed and the threshold (20 μA; Fig. 10Aa) was lower than that for the suppression of Vsacs (30 μA). When the electrode was further advanced to a depth of 3,600–5,600 μm, the threshold for Esacs increased and reached >50 μA at 4,400 μm, but ipsiversive Vsacs were still suppressed. In addition, the suppression of contraversive Vsacs appeared at 4,400–4,800 μm. In this bilateral suppression area for saccades, we examined the suppressive effect of stimulation on smooth pursuit at a depth of 4,800 μm. The suppression of smooth pursuit also occurred bilaterally, and the threshold (15 μA for both ipsiversive and contraversive smooth pursuit; Fig. 10Ab) was the same as that for the bilateral suppression of Vsacs. At a depth of 6,000–6,400 μm, Esacs and the suppression of Vsacs could not be elicited even at 80 μA. However, the suppression of only ipsiversive Vsacs again appeared at 6,800–8,000 μm. At both ipsilateral and bilateral suppression sites, high background neuronal activity was recorded, indicating that these suppression sites were located in the cerebral gray matter.

In a similar way, we examined the depth thresholds for eliciting Esacs and suppressing Vsacs to identify the suppression sites for saccades at a track interval of 500 μm in the FEF (Fig. 10B) and compared the suppressive effects of stimulation at different sites on smooth pursuit. Figure 10C shows the histological reconstruction of the stimulation tracks and the location of bilateral suppression sites for Vsacs and smooth pursuit in a representative frontal plane of the FEF. Open circles show stimulation sites where the suppression of Vsacs occurred bilaterally at thresholds of ≤40 μA. At the stimulation sites shown by filled circles, we also examined the suppressive effects of stimulation on smooth pursuit and found that both saccades and smooth pursuit were suppressed bilaterally at thresholds of ≤40 μA. The distributions were similar for these open and filled circles, indicating that the suppression sites for smooth pursuit corresponded well with those for saccades in the caudal part of the arcuate gyrus facing the inferior arcuate sulcus.

**DISCUSSION**

The present study revealed that electrical stimulation of the FEF at an intensity lower than the threshold for eliciting Esacs induced the suppression of smooth pursuit eye movements. We found that stimulation of the FEF induced two types of suppression of smooth pursuit. In the first type, stimulation in a wide area of the FEF suppressed the generation of ipsiversive, but not contraversive, smooth pursuit. This was referred to as ipsilateral suppression. In the second type, stimulation of a localized area of the FEF in the caudal part of the arcuate gyrus facing the inferior arcuate sulcus caused the suppression of both ipsiversive and contraversive smooth pursuit. This was
referred to as bilateral suppression. The FEF areas for generating these types of suppression of smooth pursuit corresponded, respectively, to the ipsilateral and bilateral suppression areas for saccades (Izawa et al. 2004a, 2004b). We previously correlated the activity of fixation neurons in the FEF while fixation was being maintained and the suppressive effects of stimulation at their locations on saccades (Izawa et al. 2009). These results suggest that the FEF plays a role in suppressing smooth pursuit as well as saccades to maintain fixation. Moreover, these findings may be consistent with the idea that the suppressive control of smooth pursuit and saccades is commonly exerted by a higher order structure, although pursuit and saccades are two different types of eye movements.

It is possible that the suppressive effect of FEF stimulation on smooth pursuit may only exist for catch-up saccades that are usually present in the initiation of pursuit. However, both the ipsilateral (Fig. 2A) and bilateral suppression of smooth pursuit (Fig. 6C) survived the elimination of catch-up saccades by step-ramp target motion. Therefore, this result indicated that stimulation of the FEF suppressed smooth pursuit per se. We further excluded the possibility that the suppression of pursuit might be attributed to unnoticeable Esacs that fix the eyes on the position (Fig. 9). If stimulation had evoked tiny contraversive Esacs, the amplitude of Esacs should have increased as the initial eye position shifted in the ipsilateral direction. Therefore, the suppression of smooth pursuit per se was again confirmed. In addition to the initiation of smooth pursuit, maintained pursuit was also suppressed by FEF stimulation. The initiation period of smooth pursuit is called the open-loop phase, whereas the period of maintained pursuit is called the closed-loop phase, during which pursuit uses visual feedback (see reviews: Keller and Heinen 1991; Lisberger et al. 1987). Therefore, the present results showed that stimulation of the FEF may suppress both the open-loop and closed-loop phases of pursuit generation.

**Stimulation Sites in the FEF for Inducing the Suppression of Pursuit and Saccades**

We examined the suppressive effects of stimulation on smooth pursuit and Vsacs in the FEF and found that the suppression sites for pursuit usually corresponded well with those for saccades. Ipsilateral suppression sites for saccades and smooth pursuit were distributed widely in the FEF (Izawa et al. 2004a), and bilateral suppression sites for saccades and pursuit were localized in the caudal part of the arcuate gyrus facing the inferior arcuate sulcus (Izawa et al. 2004b). Moreover, the thresholds for the suppression of smooth pursuit were almost the same as or slightly lower than those of Vsacs at both ipsilateral and bilateral suppression sites. Therefore, these results support the idea that the suppressive control of smooth pursuit and saccades may be exerted by a common neuronal assembly in the FEF.

In the FEF, the smooth pursuit subregion is known to be located near the spur of the arcuate sulcus (Fukushima et al.
2000; MacAvoy et al. 1991; Tian and Lynch 1996). Consistent with this previous finding, we also observed that slow eye movements were evoked in the ipsilateral direction during fixation at stimulation sites near the superior arcuate sulcus medial to the bilateral suppression area in the FEF. This smooth pursuit subregion of the FEF might not be responsible for the present suppression. Stimulation of the smooth pursuit subregion has been reported to increase the speed of ipsiversive smooth pursuit and decrease the speed of contraversive smooth pursuit (Tanaka and Lisberger 2002a). However, stimulation of the present suppression sites in the FEF did not evoke such a pattern of response. As mentioned above, the similarity of the thresholds for the suppression of smooth pursuit and saccades indicated that suppression was not due to current spread to the smooth pursuit subregion of the FEF. These results are also consistent with a previous suggestion that the smooth pursuit subregion is not a foveal extension of the saccadic FEF (Tanaka and Lisberger 2002b).

Modes of Suppression for Pursuit and Saccades

Although the suppression sites in the FEF for smooth pursuit and saccades had similar locations, the suppressive effects of stimulation on pursuit and saccades had different characteristics. Usually, stimulation at suppression sites in the FEF completely suppressed the generation of saccades at an intensity that is above the threshold for the suppression of saccades (Izawa et al. 2004a, 2004b). In contrast, such stimulation delivered during smooth pursuit without catch-up saccades tended to merely slow the movement. The difference in the suppressive effects of stimulation may reflect the difference in the neural organization of the pathways for the generation of saccades and smooth pursuit. Saccades and smooth pursuit have been assumed to be eye movements of two independent systems. For the generation of saccades, abducens motoneurons receive excitation via excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF) from the contralateral SC (Grantyn and Grantyn 1976; Izawa et al. 1999; Precht et al. 1974), which receives inputs from the FEF (Künzle and Akert 1977; Segraves and Goldberg 1987). Compared with the neural organization of saccades, that of smooth pursuit may be a highly parallel system (see reviews: Keller and Heinen 1991; Lisberger et al. 1987). In the traditional pursuit pathway, ocular motoneurons receive inputs via the vestibular nuclei and nucleus prepositus hypoglossi from the flocculus and paraflocculus of the cerebellum, which receive inputs from the MT and MST via the pontine nuclei. As an alternative pathway, vermal lobules VI and VII, which receive inputs from the FEF via the pontine nuclei and the nucleus reticularis tegmenti pontis and project to the fastigial nucleus, are involved in the generation of smooth pursuit. This pathway may convey smooth pursuit signals to ocular motoneurons through connections from the caudal fastigial nucleus via premotor neurons in the brain stem (Puchs et al. 1994; Noda et al. 1990). Brain stem premotor neurons also receive direct inputs from the pursuit subregion of the FEF (Yan et al. 2001). Although recent findings have suggested that the FEF regulates the onset of pursuit (see review in Krauzlis 2004), the MT is traditionally known to provide inputs for the initiation of pursuit (Newsome et al. 1985). Therefore, the weak suppressive effect on the initiation of pursuit may be attributed to the weak suppressive effect on pathways from the MT. A parallel system for smooth pursuit may help to generate pursuit even during stimulation at suppression sites in the FEF.

Although the above neuronal pathways for saccades and smooth pursuit are different, it has been suggested that there are common inputs for triggering saccades and pursuit, because decreases in the latency of the two types of eye movements with the early removal of a fixated target show the same dependence on the gap duration (Krauzlis and Miles 1996). Recent studies have suggested that some premotor pathways related to saccades and smooth pursuit partially overlap or share an important group of neurons at the level of the SC (Krauzlis et al. 2000) and OPNs (Keller and Missal 2003; Missal and Keller 2002). Along the pathway for the generation of smooth pursuit, inhibition at a certain level of neurons must cause the present FEF-associated suppression of pursuit. In the present study, stimulation of suppression sites in the FEF did not induce reciprocal inhibition for horizontal smooth pursuit resulting in the suppression of contraversive smooth pursuit and the facilitation of ipsiversive pursuit. This finding indicated that the present suppression of smooth pursuit was not caused by reciprocal inhibition at the level of ocular motoneurons. Therefore, this suppression might occur at the premotor rather than the motoneuronal level, most probably through FEF projections to the SC and/or the pons (Komatsu and Suzuki 1985; Künzle and Akert 1977; Segraves and Goldberg 1987; Sommer and Wurtz 2000; Stanton et al. 1988). Structures of the basal ganglia including the caudate nucleus, the subthalamus, and the substantia nigra reticulata, which are associated with the control of saccades (Cui et al. 2003; Ford and Everling 2009; Hikosaka and Wurtz 1983), may also be involved in the present suppression of smooth pursuit. Since we observed a clear decrease in eye velocity during the late stimulation period rather than the early stimulation period at both ipsilateral and bilateral suppression sites in the FEF (Figs. 3B and 7B), the incrementation of suppressive effects during stimulation may occur in the pathways for the suppression of smooth pursuit, although the exact pathways are not yet understood.

The difference between the suppression of smooth pursuit and that of saccades was also observed during oblique eye movements. After the ipsilateral and bilateral suppression of oblique pursuit, we sometimes observed that the monkey tended to correct the horizontal component before the vertical component by making catch-up saccades. This tendency was not observed after the ipsilateral and bilateral suppression of oblique saccades (Izawa et al. 2004a, 2004b). Since horizontal ocular motoneurons tend to receive large tectal inputs (Izawa et al. 1999) compared with vertical ocular motoneurons (Izawa et al. 2007), it may be easier to correct the horizontal component.

During the maintenance phase, smooth pursuit eye movements use visual feedback, which is not used for saccades. The contribution of vestibular signals is also characteristic of the pursuit system including cortical areas (Ehata et al. 2004; Fukushima et al. 2000; Kawano et al. 1984; Thier and Erickson 1992) and the brain stem (Roy and Cullen 2003). The different mechanisms for guiding the eyes during movement may result in the different suppressive effects of stimulation of suppression sites in the FEF between smooth pursuit and saccades.
Comparison With Suppression Induced by Stimulation of Other Brain Structures

Electrical stimulation of other sites in the brain has been reported to suppress smooth pursuit. Missal and Keller (2002) reported that stimulation in the region of OPNs induced a reduction in the smooth pursuit velocity, whereas the same level of stimulation applied during saccades completely stopped the movements in midflight. This qualitative difference between the suppression of smooth pursuit and that of saccades is similar to our present results with FEF stimulation. Therefore, the pathways that connect the FEF to the OPN region directly or indirectly via the SC (Segraves 1992; Segraves and Goldberg 1987; Sommer and Wurtz 2000) may contribute to FEF suppression. Basso et al. (2000) showed that stimulation of the rostral SC primarily suppressed pursuit to ipsiversive moving targets and had modest effects on contraversive pursuit. This suppressive effect of stimulation of the SC on smooth pursuit is consistent with our present results. Regarding the effects of pursuit velocity on suppression, Basso et al. (2000) reported that stimulation at a site in the rostral SC reduced ipsiversive pursuit at the highest speed, although another site in the rostral SC suppressed pursuit for both directions and was slightly better at suppressing the slower speed. Similarly, a clear trend was not observed between the FEF suppression of smooth pursuit and target velocity in the present study. Komatsu and Wurtz (1989) reported that stimulation of the foveal region of the MT and the lateral-anterior region of the MST induced eye acceleration during ipsiversive smooth pursuit and eye deceleration during contraversive smooth pursuit. This reciprocal inhibition for contraversive smooth pursuit may occur via stimulation at sites related to pursuit generation and consequently may be different from the present suppression of smooth pursuit.

Possible Role of FEF Suppression

In the brain stem, Missal and Keller (2002) showed that the neural activity of OPNs associated with fixation decreased during smooth pursuit eye movement as well as saccades. They further reported that the firing rate of OPNs was slightly correlated with eye velocity during smooth pursuit. OPNs receive input more heavily from the rostral pole of the SC (Büttner-Ennever et al. 1999; Gandhi and Keller 1997; Paré and Guitton 1994). Fixation neurons in the rostral SC increased their discharge during contraversive smooth pursuit and decreased their discharge during ipsiversive smooth pursuit (Krauzlis et al. 2000). The FEF also contains neurons that are related to fixation (Bizzì 1968; Bruce and Goldberg 1985; Suzuki and Azuma 1977). Our previous study suggested that the activity of FEF fixation neurons while fixation was maintained was correlated with the suppressive effects of FEF stimulation on saccades (Izawa et al. 2009). Moreover, the present results support the idea that a common neuronal assembly in the FEF may be responsible for the suppressive control of smooth pursuit and saccades, whereas these suppressive effects of FEF stimulation on pursuit and saccades are the result of some different processes. Further analysis of the activity of fixation neurons during smooth pursuit and saccades is necessary to understand the roles of fixation neurons in the FEF in controlling fixation and modulating eye movement systems.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Y.I. and H.S. conception and design of research; Y.I. and H.S. performed experiments; Y.I. analyzed data; Y.I., H.S., and Y.S. interpreted results of experiments; Y.I. prepared figures; Y.I. drafted manuscript; Y.I. and H.S. edited and revised manuscript; Y.I. approved final version of manuscript.

REFERENCES
