Suppression of Visually and Memory-Guided Saccades Induced by Electrical Stimulation of the Monkey Frontal Eye Field. I. Suppression of Ipsilateral Saccades

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Izawa, Yoshiko, Hisao Suzuki, and Yoshikazu Shinoda. Suppression of visually- and memory-guided saccades induced by electrical stimulation of the monkey frontal eye field. I. Suppression of ipsilateral saccades. J. Neurophysiol. 92: 2248–2260, 2004; 10.1152/jn.01021.2003. When a saccade occurs to an interesting object, visual fixation holds its image on the fovea and suppresses saccades to other objects. Electrical stimulation of the frontal eye field (FEF) has been reported to elicit saccades, and recently also to suppress saccades. This study was performed to characterize properties of the suppression of visually guided (Vsacs) and memory-guided saccades (Msacs) induced by electrical stimulation of the FEF in trained monkeys. For any given stimulation site, we determined the threshold for electrically evoked saccades (Esacs) at ±50 μA and then examined suppressive effects of stimulation at the same site on Vsacs and Msacs. FEF stimulation suppressed the initiation of both Vsacs and Msacs during and about 50 ms after stimulation at stimulus intensities lower than those for eliciting Esacs, but did not affect the vector of these saccades. Suppression occurred for ipsiversive but not contraversive saccades, and more strongly for saccades with larger amplitudes and those with initial eye positions shifted more in the saccadic direction. The most effective stimulation time for suppression was about 50 ms before saccade onset, which suggests that suppression occurred in the efferent pathway for generating Vsacs at the premotor rather than the motoneuronal level, most probably in the superior colliculus and/or the paramedian pontine reticular formation. Suppression sites of ipsilateral saccades were distributed over the classical FEF where saccade-related movement neurons were observed. The results suggest that the FEF may play roles in not only generating contraversive saccades but also maintaining visual fixation by suppressing ipsiversive saccades.

INTRODUCTION

The frontal eye field (FEF) contributes to saccade generation. Unilateral FEF lesions produce conjugate deviation of eyes to the ipsilateral side, a decrease in saccade frequency to the contralateral side, and neglect of objects in the contralateral visual field (Latto and Cowey 1971; Welch and Stuteville 1958). Electrical stimulation of the FEF evokes saccades with short latencies at low thresholds (Bruce et al. 1985; Robinson and Fuchs 1969), and the FEF contains neurons that respond to visual stimuli and neurons that discharge before saccades (Bruce and Goldberg 1985). When an interesting object appears in a visual field, a saccade occurs to that object of interest, and then visual fixation is required to hold the image of the target on the fovea. The FEF has neuronal activity related to visual fixation (Bizzi 1968; Bruce and Goldberg 1985; Suzuki and Azuma 1977). During fixation, potential saccades to other objects in the visual field must be suppressed. Therefore saccades should be suppressed with visual fixation and this suppression should be released when the line of sight changes. Although the FEF is implicated in saccade generation, there is some evidence that the FEF also exerts suppressive control on saccades. Human patients with unilateral frontal lobe lesions have difficulty in suppressing reflexive saccades to inappropriate targets in the peripheral visual field (Braun et al. 1992; Guitton et al. 1985). Lesion studies in the monkey showed that FEF inactivation increased the frequency of premature saccades to ipsilateral targets (Dias and Segraves 1999; Sommer and Tehovnik 1997). These findings may be interpreted as the impairment of suppressive function of the FEF in normal oculomotor behavior. In fact, stimulation of the FEF suppressed saccade generation (Azuma et al. 1986; Burman and Bruce 1997). Suppression produced by FEF stimulation was first reported for visually guided saccades (Vsacs) (Azuma et al. 1986). Later, however, Burman and Bruce (1997) showed that FEF stimulation mainly suppressed memory-guided saccades (Msacs) to the contralateral side. Since this latter report, the effects of FEF stimulation on the suppression of saccades have not been systematically analyzed, and the above discrepancies have not yet been resolved.

The present study was performed to investigate the properties of the suppressive effects of electrical stimulation of the FEF on saccades in trained monkeys. The results showed that FEF stimulation strongly suppressed the initiation of both Vsacs and Msacs. We found 2 types of suppression for saccades produced by stimulation of the FEF and its vicinity: suppression of ipsilateral saccades and suppression of bilateral saccades. This report describes the characteristic features of the unilateral suppression of ipsiversive Vsacs and Msacs caused by electrical stimulation of a wide area in the FEF where electrical stimulation evoked saccades (Esacs) at ±50 μA, and a companion article reports that stimulation of a localized area in the FEF suppresses saccades in all directions (Izawa et al. 2004).

These results were briefly reported previously (Izawa et al. 2001).
Methods

Experiments were performed in 2 male Japanese monkeys (Macaca fuscata), named Sui and Bell, weighing 7 and 9 kg, respectively. All animal experimentation was conducted in accordance with Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Research Council 1996), and 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. Ambient room light was dim. Each monkey was first trained to fixate 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. When the monkey released the bar only 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 because the monkey had to look at the spot to notice its brightening for rapid bar release.

When the training of the fixation task was completed, the monkey was required to make Vsacs. For this 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 because it had to observe its brightening. When the monkey released the bar during brightening of the target light, it received a reward. The monkey was also trained to make Msacs. In this task, the monkey first fixed its eyes on the center spot. During this fixation, another instruction target spot was flashed at a location on the screen for 0.5 s. This time, the monkey was required to maintain its line of sight on the center spot, while the center spot remained on. At 0.5–1.5 s after the flashed target, the center spot was turned off as a cue to make a saccade. The monkey had to make a saccade to the previously instructed location within an error window of ±3° around the visual target. Otherwise, the trial was terminated without a reward, and a new trial began. At 0.6–1.5 s after the disappearance of the center spot, the target spot that had been flashed previously was turned on again for 0.5 s to confirm a correct Msac. When the monkey released the bar only during this short brightening period, it received a reward.

Surgery

After the behavioral training, a head holder and a cylinder for a micromanipulator were implanted in the skull. The monkey was anesthetized with an intramuscular injection of ketamine hydrochloride (Ketalar, 10 mg/kg; Sankyo, Tokyo, Japan), followed by an intravenous injection of pentobarbital sodium (Nembutal, 10 mg/kg; Abbott AG, Baar/Zug, Switzerland). The latter was supplemented for maintenance, when required. Under aseptic conditions, 3 bolts for head stabilization and a 25-mm-diameter cylinder were attached to the skull over the left perirhinal cortex centered at A25, L12 for monkey Sui and at A30, L20 for monkey Bell. These implants were made of Ni-Co–Mo alloy (22A; Nippon Kinzoku, Tokyo, Japan) to minimize tissue reactions (Suzuki and Azuma 1983). After surgery, the monkey was given antibiotics (Cefamezin, 50 mg/kg per day; Fujisawa, Osaka, Japan) for 1 wk.

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 FEF with a micromanipulator (MO-95; Narishige, Tokyo, Japan) attached to the implanted cylinder. While recording neuronal activity at 200- or 400-μm intervals within the cortex, we switched from a recording circuit to a microstimulation circuit to apply microstimulation using the same electrode. Constant-current stimulation trains were generated using a Nihon Kohden ss-1945 stimulator. Trains generally consisted of 40–60 monopolar cathodal pulses of 1-ms duration at 5-ms intervals, 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 on the center spot and the threshold for evoking eye movements was determined. In subsequent stimulation trials, the monkey was instructed to make either Vsacs or Msacs, and the offset of the center fixation spot was usually accompanied by the onset of a train of stimulation pulses. Current intensities were varied systematically to determine the suppressive effects of stimulation on saccades. The effect of stimulation for eliciting Esacs during fixation was often confirmed after the suppressive effect was examined. Virtually all sites in the following descriptions were judged as being in the gray matter, based on the background neuronal activity recorded before stimulation (see Fig. 3). 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 were marked with iron deposits by passing currents (electrode positive, 400 μC) through the elgiloy microelectrode (Suzuki and Azuma 1987). Because both monkeys were being used for further experiments, we were unable to provide histological verification of recording sites.

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 vertical and horizontal 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 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 (The MathWorks, Natick, MA) programs. A preferred direction for suppression was given by a value in the fitted Gaussian function. Statistical analysis was performed with a Mann–Whitney U test for single comparisons. A Kruskal–Wallis ANOVA or a Friedman ANOVA with replication followed by a multiple comparison test (Steel method) was performed for multiple comparisons. Correlations between data sets were assessed by measuring the Pearson correlation coefficient.

Results

Suppressive effects of FEF stimulation on Vsacs

The FEF is classically defined as an area in the frontal cortex where electrical stimulation produces eye movements (Wurtz and Mohler 1976). In the monkey, such an area is located along...
the arcuate sulcus at the level of the principal sulcus (Robinson and Fuchs 1969). We could identify the location of both sulci under the dura, when we implanted the cylinder (Fig. 1Aa). Based on these anatomical landmarks, we inserted an electrode into the prearcuate area, which previous studies had considered to be the FEF (Wurtz and Mohler 1976), and confirmed that electrical stimulation of this area elicited eye movements at a low stimulus intensity (≤50 μA; classical FEF) (Fig. 1Ab). Figure 1B shows an example of eye movements produced by stimulation of the frontal cortex at site 1 in Fig. 1Ab. Stimulation was applied while a monkey fixed its eyes on a central fixation target in the fixation task (central fixation period). Stimulation of the FEF at ≤20 μA evoked no eye movement, but stimulation of the same site at 25 μA evoked saccadic eye movements with a horizontal component contraversive to the stimulated side [electrically evoked saccades (Esacs)]. These Esacs evoked by stimulation during the central fixation period were always followed by return saccades (Goldberg et al. 1986). Because Esacs were evoked in about 50% of the trials at 25 μA in this example, we regarded this stimulus intensity as the site’s threshold for evoking Esacs. At threshold, the latencies and amplitudes of these Esacs usually fluctuated, but became fixed at suprathreshold stimulus intensities. With an increase in the stimulus intensity, the latency of Esacs was slightly shortened and the amplitude of Esacs was slightly increased, whereas there was no change in the direction of Esacs. Stimulation at 50 μA constantly evoked 24.2° Esacs at an angle of 0.5° (0° is horizontal right, and the value of the angle increases counterclockwise) and with a latency of 59 ms. Thus when saccades were elicited by stimulation of ≤50 μA, we identified a stimulation site as being within the classical low-threshold FEF (Bruce et al. 1985).

The latencies of Esacs in the present study ranged from 40 to 65 ms, with 45–55 ms being typical. We systematically mapped the classical FEF, and its vicinity where electrical stimulation of >50 μA was required to evoke Esacs. At such FEF stimulation sites, we first measured thresholds for evoking Esacs (Fig. 1B), and then investigated the effects of stimulation of the same sites on Vsacs at stimulus intensities lower than the thresholds for evoking Esacs (Fig. 1C). To examine the effect of suppression, we applied a stimulus train at an intensity (15 μA in this example) lower than the Esac threshold (25 μA) at the onset of the visual target for Vsacs (Fig. 1C). This FEF stimulation delayed the generation of Vsacs ipsiversive to the stimulated side (Fig. 1Ca), but did not influence contraversive Vsacs (Fig. 1Cb). This suppression continued during the stimulation. 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 the result of a temporal factor such as the monkey’s behavioral changes or damage to brain tissue caused by passing currents. For any given set of trials, the suppressive effect of FEF stimulation was very reproducible, and FEF stimulation suppressed the initiation of ipsiversive Vsacs without influencing the amplitude or direction of Vsacs, but did not influence contraversive Vsacs. In the following sections, we

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**FIG. 1.** Effects of stimulation of the frontal eye field (FEF) on visually guided saccades (Vsacs). Aa: lateral oblique view of the frontal cortex of a monkey brain. Each circle indicates the location of a chamber for recording and stimulation of the FEF. Ab: stimulus location in the left FEF. Site 1 for B and C, and site 2 for D. IAS, inferior arcuate sulcus; SAS, superior arcuate sulcus; PS, principal sulcus. B: electrically evoked saccades (Esacs) by stimulation of the FEF (1.2 mm deep from the surface at site 1 in Ab) (a train of 60 pulses at a 5-ms interval) with increasing stimulus intensities (indicated on the left) during fixation. Vertical dotted line: onset of electrical stimulation. Top and bottom traces of individual pairs: horizontal and vertical components of eye position, respectively. Bottom trace: upward and downward steps indicate the onset and offset of electrical stimulation, respectively. C: effects of FEF stimulation on ipsiversive (a) and contraversive (b) horizontal 20° Vsacs. Top 2 and bottom 2 traces in a and b indicate horizontal and vertical components of eye movements without and during electrical FEF stimulation (15 μA, 60 pulses), respectively. Note that electrical stimulation suppressed the initiation of ipsiversive Vsacs, but not contraversive Vsacs. Stimuli were applied at the same site as in B. D: effects of varying the number of stimuli on the suppression of ipsiversive horizontal Vsacs. Zero to 200 pulses of stimulus at an interval of 5 ms (stimulus intensity, 24 μA) were applied to site 2 in Ab (4 mm deep from the surface) as shown in the bottom trace in each condition. In C and D, vertical dotted lines indicate the onset of a target light, and the bottom-most traces in individual records show behavioral event indicators. Upward step indicates both target onset for Vsac and the onset of electrical stimulation. Second downward smaller step indicates the cessation of stimulation, but with the target light on. Time calibration in C applies to both B and C, and the saccade amplitude calibrations in B apply to B–D.
will describe features of the characteristic suppression of ipsilateral Vsacs and also Msacs induced by electrical stimulation of the FEF in more detail.

**STIMULUS PARAMETERS FOR EFFECTIVE SUPPRESSION OF VSACS.** To find the most effective stimulus parameters for suppression of saccades, we systematically examined the effects of varying stimulus parameters on the suppression of Vsacs. Figure 1D shows an example of the effect of varying the train duration on Vsac 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, the stimulus intensity of 24 μA for 200 ms, which was well below the threshold for evoking Esacs (50 μA), was strong enough to suppress the initiation of Vsacs. A train of 10 and 20 stimulus pulses slightly delayed the onset of Vsacs and a train of 30 or more stimulus pulses clearly delayed the onset of Vsacs. Vsacs were completely suppressed during stimulation for up to 1 s (200 pulses), and suppression continued for about 50 ms after the end of stimulation. As in this case, stimulation at a sufficiently suprathreshold intensity generally caused the suppression of Vsacs during stimulation and for up to about 50 ms after stimulation offset. However, suppression did not always continue during stimulation, but rather depended on the stimulation site and intensity, so that Vsacs with delayed onsets in some trials occurred during prolonged stimulation (500 or 700 ms). We examined the effect of the stimulus pulse interval on the suppression of Vsacs (not shown). Pulse intervals were varied from 3.3 to 9 ms, whereas the stimulus intensity and train length were kept constant. The suppression of Vsacs was weak using a stimulus train with a 3.3-ms interval, but stable using a stimulus train with a 5-ms interval. For intervals of 6–9 ms, the suppressive effect was the same as for the 5-ms interval, or tended to fluctuate between trials with sufficient and weak suppression. Thereafter, the pulse interval was fixed at 5 ms in later experiments.

To examine the effects of varying the stimulus intensity on the suppression of ipsiversive and contraversive Vsacs, stimulus intensities were increased from 0 to 50 μA at a 5-μA interval (Fig. 2). Although no effect appeared at ≤20 μA, a delay in the initiation of ipsiversive 20° Vsacs occurred and the fluctuation of the latencies of individual Vsacs increased at 25 μA (Fig. 2, left column). When the stimulus intensity was increased to 45 μA, the complete suppression of Vsacs occurred during stimulation and this suppression persisted for about 50 ms after stimulation offset. With a further increase to 50 μA, the suppression became stronger, although Esacs were evoked in some trials. The threshold for suppression was defined as the least stimulus current required to produce an increase in the saccade latency that was more than 2 SDs of the control saccade latency. The mean ± SD of the latency of control Vsacs was 181 ± 24 ms in monkey Sui (n = 261), and 188 ± 19 ms in monkey Bell (n = 245). Based on this criterion, we determined that the threshold for suppression was 25 μA in the example in Fig. 2. At the same stimulation site, contraversive Vsacs were not suppressed even at 50 μA, but the latencies of contraversive 20° Vsacs at 35 μA (median 137 ms) or more tended to be shorter than in control (median 164 ms) (U test, P < 0.01 at ≥35 μA). In spite of the effects of stimulation on Vsac initiation, there was no significant differ-

![FIG. 2. Threshold for FEF-associated suppression of Vsacs. Stimulation (60 pulses) was applied with increasing stimulus intensity (indicated as numerals on the left) at the onset of visual target for ipsiversive (left column) and contraversive (right column) horizontal 20° Vsacs. Threshold for contraversive Esacs at this stimulation site was 50 μA. Note that the bottom traces at 45 and 50 μA show vertical components of the eye movements.](http://jn.physiology.org/)

ence in the amplitude or direction of ipsiversive Vsacs (U test, P = 0.33 and P = 0.79, respectively) and contraversive Vsacs (U test, P = 0.17 and P = 0.51, respectively) in control and stimulation trials (45 μA), suggesting that the accuracy of Vsacs was maintained. The amplitude and direction of contraversive Vsacs were sometimes affected, when stimulation current was increased very close to threshold for Esacs. However, they were not usually affected, given that the thresholds for suppressing Vsacs were well below the threshold for evoking Esacs at most stimulation sites. Therefore such interaction will not be described in detail here, but the interaction between Vsacs and Esacs will be reported in a companion paper (Izawa et al. 2004).

**DEPTH-THRESHOLD CURVES FOR ELICITING EASC S AND SUPPRESSING VSACS.** In every track, we advanced an electrode while recording background neuronal activity and examined the effects of stimulation at 200- or 400-μm intervals for eliciting Esacs, and then for suppressing Vsacs. Figure 3 shows a typical example of depth-threshold curves for eliciting Esacs (dotted line) and suppressing Vsacs (solid line). On the left, background neuronal activity is shown to indicate whether recording sites were located in the cerebral gray matter or white matter. In this track, Esacs were evoked at 400 μm, and thresholds for Esacs decreased with advancement of the electrode, reaching the minimum (25 μA) at depths of 1,200 and 1,600 μm, where high background neuronal activity was recorded. The thresholds then increased as the electrode was further advanced. The thresholds for suppressing ipsiversive Vsacs were almost parallel to those for eliciting Esacs (dotted line), and lower by 7–40 μA (solid line). The lowest threshold for suppression was 12 μA at a depth of 1,600 μm. In the deeper part of the penetration, where background activity was very slight, no effect of stimulation was observed for Esacs or
Vsacs. As in this example, the lowest thresholds for suppressing Vsacs were always found in the gray matter where high background neuronal activity was recorded. To confirm that these suppression sites were located in the classical FEF, we recorded from single cells and examined their neuronal activity in relation to visual stimuli and saccadic eye movements. Figure 3B shows activity of a neuron observed at such an FEF site. This neuron discharged before Msacs and did not respond to visual stimuli, so that it was classified as a movement neuron according to previously published criteria (Bruce and Goldberg 1985). Because saccade-related movement neurons like this neuron were found in tracks including the suppression sites, it was concluded that the suppression sites were located in the classical FEF.

The delay in the initiation of ipsiversive Vsacs caused by FEF stimulation depended on the stimulus intensity and the stimulation site. At some stimulation sites, a suppressive effect was observed at <10 μA, even though Esac thresholds were >50 μA, and the difference between the thresholds for Esac generation and Vsac suppression was more than 40 μA. At some other FEF sites, stimulation evoked Esacs, but stimulation of the same sites at an intensity just below the Esac threshold had no suppressive effect on Vsacs. The suppression of ipsiversive Vsacs was found in 293 of 302 tracks in which electrical stimulation evoked contraversive Esacs at ≤50 μA, indicating that suppression sites were prevalent in the classical FEF.

**SUPPRESSIVE EFFECTS OF FEF STIMULATION ON VSACS WITH DIFFERENT DIRECTIONS.** To determine the effective direction of suppression, we examined the suppressive effects of FEF stimulation on Vsacs by changing their directions to 8 or 10 different directions with the amplitude of Vsacs (10°) fixed (Fig. 4). The latencies of Vsacs were significantly longer in stimulation trials than in control trials (Friedman ANOVA, \( P < 0.0001 \)). Suppression occurred predominantly for Vsacs with an ipsilateral horizontal component (\( U \) test, \( P < 0.05 \) for 135, 157.5, 180, 202.5, and 225°) (Fig. 4A, a–e), and only slightly for vertical Vsacs with a downward (\( U \) test, \( P < 0.05 \)) (Fig. 4Af) or upward direction (Fig. 4Aj). In contrast, suppression was not observed for Vsacs with a contralateral horizontal component (\( U \) test, \( P > 0.05 \) for 315, 0, and 45°) (Fig. 4B, g–i), but their latencies tended to be rather shortened by 5–30 ms. The correlation between the latencies of horizontal and vertical components of individual oblique Vsacs was highly significant (\( y = 0.999x + 2.72, r = 0.99, P < 0.001, n = 23 \)), and the slope (0.99) and intercept (2.72) of a regression line was not significantly different from 1 and 0 (\( t \) test, \( P = 0.85 \) and \( P = 0.66 \)), respectively. Therefore both the horizontal and vertical components of individual Vsacs were always synchronously suppressed by stimulation. The preferred direction for the suppression of Vsacs was determined by using the difference in latency between Vsacs in stimulation and control trials (dotted line in Fig. 4B) as an index of the strength of the suppression in each direction because the latencies of Vsacs in different directions were varied in the control. In the example in Fig. 4, suppression showed a preference for the ipsilateral downward direction (198.4°). To examine the relationship between the directions of Esacs and suppression, we increased the stimulus intensity at the same stimulation site to evoke contraversive Esacs. Esacs were evoked at a threshold of 50 μA to the contralateral downward direction (340.1°) (Fig. 4B, arrow). We compared the preferred direction of suppression and the Esac direction at all 14 stimulation sites where similar analysis was performed. The preferred direction of suppression was nearly opposite the direction of Esacs at 8 stimulation sites, whereas at the other 6 sites the vertical components were in the same direction and the horizontal components were opposite.

It is possible that the laterality in the suppression of Vsacs might depend on the internal status of the monkey rather than on electrical stimulation itself. Among possible factors that might affect the internal status of the monkey, background visual input could be excluded because we used a tangent
screen that was evenly illuminated. On the other hand, auditory input had laterality, since a solenoid bulb that regulated the supply of juice was fixed to the right side (contralateral to the stimulation side) of the monkey. However, this factor could also be excluded because a comparison of suppressive effects with the solenoid bulb on the monkey’s right and left sides showed no difference in latency at any of the 3 stimulation sites examined.

SUPPRESSIVE EFFECTS OF FEF STIMULATION ON VSACS WITH DIFFERENT AMPLEUTIES. To investigate the suppressive effects of FEF stimulation on Vsacs with different amplitudes, the Vsac amplitude was changed from 5 to 20° at intervals of 5° (Fig. 5).

Under the control condition with no stimulus, the latencies of Vsacs tended to decrease as their amplitudes increased (Fig. 5A, left column). This inverse relationship between the latency and amplitude of Vsacs is consistent with a previous observa-

![Figure 4](image-url)

**FIG. 4.** Suppressive effects of FEF stimulation on Vsacs with different directions. A: 10° Vsacs with 10 directions in the control and during FEF stimulation. a–j correspond to target directions of 135, 157.5, 180, 202.5, 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°. Top and bottom pairs of traces in individual records indicate control and stimulation (30 μA, 80 pulses) trials, respectively. In the top and bottom pairs, top and bottom traces show the horizontal and vertical components of eye position, respectively. Threshold for Esacs at this stimulation site was 50 μA. Bottom trace (in each column): behavioral event indicator in the same manner as in Fig. 1. B: polar representation of median latencies of Vsacs in the control (thin line) and FEF stimulation trials (thick line) shown in A. Letters a–j correspond to those in A. Strength of the suppression of Vsacs was defined as the difference between the Vsac latencies in the control and stimulation trials for each saccadic direction (dotted line). Arrow: direction of Esacs.

![Figure 5](image-url)

**FIG. 5.** Suppressive effects of FEF stimulation on Vsacs with different amplitudes. A: example of the suppression of horizontal 5–20° Vsacs to the right (R) and left (L). Stimuli (60 pulses) were applied to the left FEF at intensities indicated at the top. Threshold for contraversive Esacs at this stimulation site was 50 μA. Amplitude of the Esac was 22.8° in the direction of 11.1°. B: latencies of horizontal 5–20° Vsacs affected by FEF stimulation with different stimulus intensities. Abscissa: Vsac amplitudes. Ordinate: medians and quartiles of the Vsac latencies. Note that only the onsets of ipsiversive Vsacs were delayed.
tion that the shorter the latency, the greater the amplitude of saccades evoked by stimulation of the superior colliculus (SC) (Stanford et al. 1996). When the stimuli were applied, the latencies of ipsiversive Vsacs increased (Friedman ANOVA, $P < 0.0001$; Steel method, $P < 0.05$ for $\geq 10 \, \mu A$), but those of contraversive Vsacs did not (Friedman ANOVA, $P = 0.10$). FEF stimulation at $20 \, \mu A$ suppressed ipsiversive Vsacs with amplitudes of 15 and 20°, whereas the same stimulation did not suppress contraversive Vsacs of any amplitude (Fig. 5A, middle column). At 30 $\mu A$, all ipsiversive Vsacs with amplitudes of 5–20° were suppressed, and suppression was greater in Vsacs with larger amplitudes (Fig. 5A, right column). At 40 $\mu A$, stimulation strongly suppressed ipsiversive Vsacs of all amplitudes and suppression continued for about 50 ms after the end of stimulation, but contraversive Vsacs were not suppressed at all by the same stimulation. The strength of the ipsilateral suppression depended on the saccade amplitude, and was saturated at a stronger stimulus intensity at all of the 13 stimulation sites tested. As shown in Fig. 5B, ipsiversive Vsacs with larger amplitudes were suppressed at lower thresholds by FEF stimulation, whereas a similar trend was not seen for contraversive Vsacs of any amplitude. Even when the preferred direction of suppression was almost opposite the Esac direction, the suppression was weaker for larger Vsacs irrespective of the amplitudes of Esacs.

SUPPRESSIVE EFFECTS OF FEF STIMULATION ON VSACS WITH DIFFERENT INITIAL EYE POSITIONS. In the experiments described so far, Vsacs were always initiated with the eyes at the center position. To investigate the effects of the initial eye position on Vsac suppression, the initial eye position was changed from contralateral 20° to ipsilateral 20° at intervals of 5° at 6 stimulation sites, whereas the Vsac amplitude was fixed at 10° (Fig. 6). In the control, the latencies of Vsacs were almost constant when the initial eye positions were opposite the Vsac direction, but increased as the initial eye position shifted in the direction of Vsacs (Kruskal–Wallis ANOVA, $P < 0.01$ for each direction). Stimuli applied at different intensities significantly increased the latencies of ipsiversive Vsacs with different initial eye positions (Friedman ANOVA, $P < 0.0001$; Steel method, $P < 0.05$ for $\geq 20 \, \mu A$). Stimulation of the left FEF at 30 $\mu A$ caused a delay in the initiation of ipsiversive Vsacs with an initial eye position of right 20°, and this delay increased when the initial eye position was shifted from right 20° to left 20° (Fig. 6A). At 40 $\mu A$, the delay for Vsacs with contralateral initial eye positions was greater, whereas at 20 $\mu A$, the delay with ipsilateral initial eye position was smaller than that at 30 $\mu A$ (Fig. 6C). These results showed that the more the initial eye position was shifted toward the direction of ipsiversive Vsacs from the center position, the stronger the suppression of the Vsacs (Fig. 6, A and C). In contrast, the same stimulation did not delay the onset of contraversive Vsacs with any initial eye position, but rather shortened the latency of contraversive Vsacs with any contralateral initial eye position (Friedman ANOVA, $P < 0.001$) (Fig. 6, B and D). A similar tendency was observed at all of the 6 stimulation sites examined.

SUPPRESSIVE EFFECTS OF STIMULUS TIMING ON VSACS. To determine the most effective stimulus timing for the suppression of ipsiversive Vsacs, we changed the timing of stimulation onset relative to visual target onset. The time course of suppression was examined at 17 stimulation sites by changing the interval between stimulation onset and visual target onset at 10- or 20-ms intervals (Fig. 7A). The stimulus duration and intensity were fixed at 200 ms and 40 $\mu A$, respectively. Stimulation given at intervals from 140 to 160 ms suppressed Vsacs in some trials, and stimulation at intervals of $\leq 130$ ms completely suppressed Vsacs during stimulation in all trials. Non-suppressed Vsacs at 140–160 ms tended to occur earlier than Vsacs in the control. Because the latencies of Vsacs fluctuated even in the control, suppressed Vsacs at these intervals were most likely Vsacs that should have occurred at longer onset latencies. Nonsuppressed Vsacs generated at shorter latencies had almost the same amplitudes as in the control, but those with average latencies had slightly depressed amplitudes. Figure 7B shows the time course of Vsac latencies in Fig. 7A (thick line) and in the control without stimulation (thin line). Suppression of Vsacs started at an interval of 150 ms, and the delay of Vsacs became maximal at an interval of 130 ms. The Vsac latency decreased with regard to the stimulation onset as the interval was further decreased. The systematic effects of varying the stimulus intensity on the time course of suppression at the same stimulation site are illustrated in Fig. 7C. The time courses of suppression for 30 and 40 $\mu A$ were very
similar and peak suppression occurred at 130 ms. The time course for 20 μA had a peak at 130 ms, but the Vsac latencies returned to almost the control level at 110 ms. At 10 μA, a weak suppressive effect was observed only at 150–130 ms. These results showed that the latest timing of stimulus train onset for effective suppression was about 130 ms after visual target onset, which corresponded to about 50 ms before Vsac onset. Similar results were obtained at all of the 17 stimulation sites tested. Stimulation before this timing suppressed Vsacs in all trials, whereas stimulation after this timing did not suppress Vsacs, except when Vsacs that should have occurred at a longer onset latency were occasionally suppressed.

To further understand where this Vsac suppression occurs among the cortical or subcortical structures for generating Vsacs, we compared the effective timings for Vsac suppression in 2 different ways. An example shown in Fig. 7, D and E is typical of results obtained from 4 stimulation sites tested. As in Fig. 7A, the onset of stimulus train with a fixed duration and intensity (200 ms, 47 μA) was changed from 180 to 80 ms after onset of the visual target at 5- or 10-ms intervals (Fig. 7D). As the interval between stimulation onset and visual target onset was decreased from 180 to 135 ms, Vsac latency was delayed in some trials, and at intervals of ≤130 ms, Vsacs were almost completely suppressed in more than half of the trials during stimulation. In the second method, the onset of a stimulus train with a fixed stimulus intensity (47 μA) was adjusted to coincide with the visual target onset, and the number of stimuli at a 5-ms interval was increased (Fig. 7E, inset). An increase in the number of stimuli gradually delayed the onset of Vsacs. To determine the earliest effective stimulus for suppression, the latencies of Vsacs were plotted relative to the stimulus train duration (Fig. 7E). The delay in Vsac onset at a train duration of 125 ms (26 pulses) or more was statistically significant (Kruskal–Wallis ANOVA, P < 0.0001; Steel method, P < 0.05). Therefore the earliest onset of the suppression of ipsiversive Vsacs (~55 ms before Vsac onset) was slightly earlier than the latest onset of a stimulus train (~50 ms before Vsac onset).

Suppressive effects of FEF stimulation on Msacs

So far, we have described the suppressive effects of FEF stimulation on Vsacs. In this section, we describe the properties of the suppression of Msacs caused by FEF stimulation and compare the suppression on Vsacs with the suppression on Msacs. We first identified suppression sites in the FEF for ipsiversive Vsacs, as described above, and then examined the effects of stimulation at the same sites on Msacs. In the example in Fig. 8A, the onset of ipsiversive Vsacs was delayed at a threshold of 15 μA, and Esacs were evoked at 40 μA in some trials. Stimulation of the same FEF site at the same stimulus parameters also suppressed ipsiversive Msacs, but not contraversive Msacs (Fig. 8B). The suppression threshold for ipsiversive Msacs was 15 μA, which was the same as that for ipsiversive Vsacs. Thresholds for the suppression of Vsacs and Msacs were very similar at 6 stimulation sites, but were slightly different at 4 stimulation sites (lower for Vsacs, 3 sites; lower for Msacs, 1 site). However, the correlation between them was significant (γ = 0.99x + 7.31, r = 0.80, P < 0.01, n = 10). In addition, the depth-threshold curves for the suppression of Msacs and Vsacs were usually similar along individual penetration tracks (not shown).

The suppressive effects of FEF stimulation on Vsacs and Msacs with various directions were compared by examining 8 directions for Vsacs and Msacs with the saccade amplitude fixed at 10° (Fig. 9). Stimulation (30 μA, 60 pulses) strongly suppressed Vsacs with an ipsilateral horizontal component (Fig. 9A, a–c) and vertical Vsacs in the downward (Fig. 9Ad) and upward directions (Fig. 9Ah), but did not suppress Vsacs with a contralateral horizontal component (Fig. 9A, e–g).
Stimulation of the same site with the same stimulus parameters also strongly suppressed Msacs with an ipsilateral horizontal component (Fig. 9B, a–c) and vertical Msacs in the downward (Fig. 9Bd) and upward directions (Fig. 9Bh). Although a suppressive effect was not observed for Msacs with a contralateral horizontal component (Fig. 9Be–g), the latencies of Msacs in the contralateral (0°) and contralateral downward (315°) directions tended to be decreased by stimulation. Polar plots of the latencies of Vsacs and Msacs (Fig. 9, C and D) showed that the directional preferences in the suppression of both Vsacs and Msacs appeared to be very similar. Similar results regarding the effects of varying the saccade direction on saccade latency were obtained at all 5 stimulation sites tested.

The effect of FEF stimulation on the vector of Msacs was examined by plotting the endpoints of Msacs for 10° target positions in 8 directions with and without stimulation, and this effect was compared with the effect of the same stimulation on the vector of Vsacs (not shown). Neither the amplitudes nor directions of the Vsacs in any direction in stimulation trials were significantly different from those in control trials (U test, \( P > 0.05 \) and \( P > 0.05 \), respectively, for each target location) at 5 stimulation sites. At most of these stimulation sites (\( n = 4 \)), the amplitudes and directions of Msacs were not affected by stimulation (U test, \( P > 0.1 \) and \( P > 0.1 \), respectively, for each target location), although the vector of Msacs was slightly hypometric (U test, \( P = 0.04 \)) at one stimulation site (\( n = 1 \)). These findings about the similarity of suppressive effects on Vsacs and Msacs suggest that stimulation of the FEF should suppress the common pathway for both Vsac and Msac.

**DISCUSSION**

The present study revealed that electrical stimulation of the classical FEF at an intensity lower than the threshold for eliciting Esacs completely suppressed the initiation of ipsiversive, but not contraversive, Vsacs and Msacs for up to about 50° visual targets in the control and during FEF stimulation. a–h correspond to target directions of 135, 180, 225, 270, 315, 0, 45, and 90°, respectively. Top and bottom pairs of traces in individual records indicate control and stimulation (30 µA, 60 pulses) trials, respectively. Arrangement of horizontal and vertical components of eye position is the same as in Fig. 4. C and D: polar representation of median latencies of Vsacs (C) and Msacs (D) in control (thin line) and stimulation (thick line) trials shown in A and B, respectively. Letters a–h correspond to those in A and B.

**FIG. 8.** Suppressive effects of FEF stimulation on Vsacs and Msacs. A and B: effects of varying the stimulus intensity on ipsiversive and contraversive 10° Vsacs (A) and on ipsiversive and contraversive 10° Msacs (B). Stimulation (60 pulses) with increasing stimulus intensities (indicated on the left) was applied to the same FEF site for A and B. In B, stimuli were applied at the offset of the central fixation point for triggering saccades. Note that contraversive Esacs were evoked at 40 µA at this stimulation site.

**FIG. 9.** Suppressive effects of FEF stimulation on Vsacs and Msacs with different directions. A and B: Vsacs (A) and Msacs (B) with 8 directions to 10° visual targets in the control and during FEF stimulation. a–h correspond to target directions of 135, 180, 225, 270, 315, 0, 45, and 90°, respectively. Top and bottom pairs of traces in individual records indicate control and stimulation (30 µA, 60 pulses) trials, respectively. Arrangement of horizontal and vertical components of eye position is the same as in Fig. 4. C and D: polar representation of median latencies of Vsacs (C) and Msacs (D) in control (thin line) and stimulation (thick line) trials shown in A and B, respectively. Letters a–h correspond to those in A and B.
ms after stimulation offset, and did not affect the vector of the saccades. Suppression produced by electrical stimulation of the FEF was first reported for Vsacs (Azuma et al. 1986). Later, however, Burman and Bruce (1997) reported that Vsacs were less severely suppressed than Msacs and contraversive saccades were usually more strongly suppressed than ipsiversive saccades. In their study, low-intensity stimulation (20–50 μA, 350- to 450-ms trains) suppressed at least one of the 3 task-related saccades (Vsac, Msac, and antisaccade) at 18 of 54 sites where electrical stimulation did not elicit Esacs or any other eye movement. At these “pure suppression” sites, Msacs were most dramatically suppressed and often hypometric, and contraversive saccades were usually more strongly suppressed than ipsiversive ones. At their “pure suppression” sites, cells with foveal or postsaccadic responses were most prevalent.

Burman and Bruce (1997) also reported that at many FEF sites (their saccade sites) at which low-threshold Esacs could be elicited (12 of 23 sites tested), stimulation produced suppression (their saccade sites) at which low-threshold Esacs could be elicited (12 of 23 sites tested), and only ipsiversive Msacs and Vsacs were suppressed, 4) locations of such suppression sites were widely distributed over a classical FEF, and 5) saccade-related movement neurons were prevalent. In contrast, the present suppression is more likely to be similar to their suppression at saccade sites in that the suppression occurs at the sites where Esacs were evoked at ±50 μA.

However, there are several reasons why the present suppression differs from that reported by Burman and Bruce (1997). The most important reasons may be related to kinds of suppressed saccades and threshold and directionality of suppression: we found that our suppression occurred equally on both Vsacs and Msacs at stimulus intensities well below the threshold for eliciting Esacs at each site and only ipsiversive saccades were suppressed. Burman and Bruce (1997) reported that at 4 of 5 saccade sites tested with subthreshold currents for eliciting Esacs, suppression occurred on saccades in all directions but the direction of the Esac in which direction saccades were facilitated, and the accuracy of suppressed saccades was often altered. Therefore they concluded that task-related saccades whose vectors differed from the vector of Esac elicited at a stimulation site were suppressed by stimulation of the same site. Although we found that contraversive saccades were facilitated at some stimulation sites (Figs. 4 and 9), suppression occurred only on ipsiversive saccades even at such sites.

As to the relation between the Esac amplitude and the amplitudes of suppressed saccades, we found that initiation of the larger Msacs and Vsacs was more strongly suppressed irrespective of the amplitude of the Esac elicited at the same stimulation site. Furthermore, the accuracy of Vsacs and Msacs was not usually affected at our suppression sites. At their (Burman and Bruce 1997) saccade sites some suppression was observed at stimulus intensities subthreshold for eliciting Esacs, but they also reported that similar suppression effects of stimulation were observed in trials when Esacs were elicited. In these trials, the interaction between Esacs and Vsacs or Msacs has to be taken into consideration. This problem will be dealt with in an accompanying paper (Izawa et al. 2004) with respect to the suppression of contraversive saccades. Some methodological differences may account for the differences obtained in the present and Burman and Bruce (1997) experiments. Our experiments usually involved the delivery of 40–60 monopolar cathodal pulses of 1-ms duration at 5-ms intervals. On the other hand, in the Burman and Bruce (1997) experiments, biphasic pulses with each pulse pair 0.4 ms in duration were used and train duration was 350–450 ms, although the frequency used seemed not to be described. The latencies of saccades of the monkeys used in the 2 experiments also differed significantly. In the Burman and Bruce (1997) paper, latencies of Vsacs are 274–344 ms but are about 180 ms in our experiments. The stimulation site in the FEF may also contribute to the difference in the laterality of suppression. Most of the present stimulation sites for suppression were distributed widely over the classical FEF area where electrical stimulation elicited Esacs at low intensities, whereas Burman and Bruce (1997) reported that their stimulation sites for suppression were located near the spur of the arcuate sulcus, similar to the smooth pursuit subregion of the FEF (MacAvoy et al. 1991; Tanaka and Fukushima 1998).

The duration and intensity of FEF stimulation influenced the duration of the suppression, but did not influence the accuracy of Vsacs. The signals that convey information about the metrics of a saccade can be dissociated from the saccadic trigger signal (Fuchs et al. 1985; Sparks et al. 1987). Therefore the present result suggests that FEF stimulation may have a suppressive effect on the saccade trigger system rather than the metric controlling system. The preferred direction for the suppression of ipsiversive Vsacs was almost 180° opposite the direction of Esacs at 8 of 14 stimulation sites, but was different from directly opposite the Esac direction at 6 of 14 sites. This latter finding supports the interpretation that unilateral suppression of Vsacs is not ascribed to reciprocal inhibition that occurs at a motoneuronal level by inhibitory burst neurons (IBNs) activated by FEF stimulation. The pathway responsible for FEF-associated suppression must either inhibit premotor neurons that control oblique saccades or simultaneously inhibit horizontal and vertical premotor neurons (Büttner-Ennever and Büttner 1988; Fuchs et al. 1985) because FEF stimulation synchronously suppressed the onsets of the horizontal and vertical components of ipsiversive saccades. Stimulation of the FEF increased the latencies of ipsiversive Vsacs at intensities lower than those that evoked Esacs at each stimulation site, but decreased the latencies of contraversive Vsacs. This finding suggests that FEF stimulation may facilitate the activity of neurons in the pathway for generating contraversive Vsacs, and reciprocally suppress the activity of neurons in the pathway for generating ipsiversive Vsacs. Abducens motoneurons receive excitation by excitatory burst neurons (EBNs) from the contralateral SC and inhibition by IBNs from the ipsilateral SC (Grantyn and Grantyn 1976, 1982; Izawa et al. 1999; Precht et al. 1974). Therefore the FEF suppression of ipsiversive Vsacs may be attributable to activation of this reciprocal inhibition by the SC. Reciprocal inhibition at the level of ocular motoneurons should result in a reduction of Vsac amplitude as well as a delay of Vsac initiation, but the present FEF stimulation did not influence the amplitude of Vsacs. In addition, the present results showed the stronger suppression of larger ipsiversive Vsacs. Larger ipsiversive Vsacs are not more easily suppressed at the motoneuronal level by reciprocal inhibition by IBNs that
might be activated by FEF stimulation, given that ipsilateral abducens motoneurons receive stronger excitation by the SC from the contralateral FEF for the larger Vsacs. Furthermore, we found that Vsacs with initial eye positions shifted more in the saccadic direction were more strongly suppressed. By shifting the initial eye position in the direction of Vsac from the center, the motoneuronal membrane potential is depolarized, so that a decrease in the rising slope of excitatory input may result in delaying spike initiation ( Eccles 1964). If FEF stimulation had activated contralateral IBNs by the SC and caused hyperpolarization in ipsilateral abducens motoneurons, this change in membrane potential should have decreased the latency of ipsiversive Vsacs (Izawa et al. 1999). Accordingly, these findings suggested that the reciprocal inhibition at the motoneuronal level did not largely contribute to the present suppression, and that Vsac suppression might occur at a pre-motor level.

The earliest and latest effective FEF stimulation for Vsac suppression were about 125 and about 130 ms after target onset (i.e., ~55 and ~50 ms before saccade onset), respectively. In the FEF, a visual stimulus activates visual neurons at latencies of about 90 ms (Bruce and Goldberg 1985), whereas movement neurons start firing about 150 ms after target onset (Bruce and Goldberg 1985) and about 100 ms before Vsac onset (Segraves and Park 1993). Taking into account the latencies of these neurons, it is safe to conclude that FEF stimulation suppressed neurons in the efferent pathway from the FEF to ocular motoneurons, rather than those in the afferent pathway from the retina to the FEF. Candidates for such suppression are the FEF, the SC, and the paramedian pontine reticular formation (PPRF). Inhibition of the contralateral FEF might be responsible for the suppression of ipsiversive Vsacs, since Schlag et al. (1998) showed that movement-related neurons in the FEF were inhibited by electrical stimulation of the contralateral FEF at a latency of 5–20 ms. The latencies of FEF-evoked Esacs ranged from 40 to 65 ms, with 45–55 ms being typical. Using much higher currents, Robinson and Fuchs (1969) found that FEF-Esacs had short latencies of 15–25 ms, and Bruce et al. (1985) reported Esac latencies of 20–60 ms. However, natural signals for Vsacs from the FEF take more time to generate saccades than electrically driven signals. Therefore the FEF stimulation must be given ≥45–85 ms before the onset of Vsacs for suppression of the contralateral FEF. Movement neurons in the FEF should have already started firing (~100 ms before Vsac onset) at the time of the latest effective FEF stimulation for suppression (~50 ms before Vsac onset). However, inhibition of contralateral FEF might be considered as a possible mechanism for suppression because the stimulation pulses may affect saccades on the tail of the reaction time distribution. The present data suggest that the SC and PPRF are more likely candidates for the present FEF suppression. Deeper-layer neurons in the SC show burst spike activity ≥30–50 ms before saccade onset (Sparks et al. 1976; Wurtz and Goldberg 1972). Electrical stimulation of the SC elicits Esacs with a latency of 20–30 ms (Azuma et al. 1996; Robinson 1972; Schiller and Stryker 1972).

As discussed previously, the synchronous suppression of horizontal and vertical components of Vsacs may be attributed to the suppression of neuronal activity in the SC. Direct projection from the FEF to the ipsilateral SC has been well established (Künzle and Akert 1977; Segraves and Goldberg 1987), and inhibitory connections have been reported between the bilateral superior colliculi (Munoz and István 1998). Schlag-Rey et al. (1992) reported that FEF microstimulation that was suprathreshold for evoking saccades of a given vector inhibited SC saccade cells encoding a different vector. Schiller et al. (1987) showed that ablation of the SC increased the latency of contraversive saccades and the proportion of express saccades ipsiversive to the collicular lesion, probably as a consequence of the disruption of intercollicular inhibitory connections. This suggestion is consistent with the present finding that FEF-associated suppression of Vsacs may occur at the level of the SC. Stanford et al. (1996) suggested that there must be at least 3 independent readouts of collicular activity; one that specifies saccade direction and amplitude, a second that specifies the speed of the movement, and a third that triggers the movement. The FEF suppression of ipsilateral saccades could occur by inhibiting this third mechanism in the ipsilateral SC, so that inhibition of omnipause neurons (OPNs) will be suppressed at the onset of saccades. Although the exact inhibitory neural connections within the SC are not yet fully understood, these previous findings suggest that the SC may contribute at least in part to the present FEF-associated suppression. Input from the basal ganglia may be another source of inhibition in the SC. Activation of the FEF inhibits neurons in the substantia nigra reticulata (SNr) by caudate neurons, thereby disinhibiting ipsilateral SC neurons (Hikosaka and Wurtz 1983), and therefore may influence inhibition of the contralateral SC indirectly by the intercollicular connection (Munoz and István 1998; Schiller et al. 1987). Ipsilateral EBNs in the PPRF may be suppressed by FEF stimulation. Stimulation of the PPRF produces saccadeliike eye movements at an EMG latency of about 3 ms (Cohen and Komatsuzaki 1972). EBNs show a burst of activity 8–10 ms before saccade onset (Luschei and Fuchs 1972). Stimulation of the FEF may activate contralateral EBNs, which produce depolarization subthreshold for generating spikes in contralateral abducens motoneurons. The same FEF stimulation may also activate contralateral IBNs, which in turn produce hyperpolarization in ipsilateral EBNs (Strassman et al. 1986; Yoshida et al. 1982). This hyperpolarization may reduce the number of ipsilateral firing EBNs, which in turn causes membrane potentials of ipsilateral abducens motoneurons to become subthreshold for firing. Therefore this IBN inhibition of EBNs may be responsible for the suppression of ipsiversive Vsacs, if it is much stronger than on abducens motoneurons. Another possibility is the inhibition of EBNs by OPNs. EBNs receive tonic inhibition from OPNs at rest (Keller 1974; Ohgaki et al. 1987). Stimulation of the FEF, which evokes Esacs, inhibits OPNs and thereby disinhibits both EBNs and IBNs (Segraves 1992). However, stimulation of the FEF may activate OPNs directly (Stanton et al. 1988) or indirectly by the SC (Gandhi and Keller 1997; Langer and Kaneko 1990; Paré and Guittton 1994; Raybourn and Keller 1977), and these OPNs may inhibit EBNs ipsilateral to the FEF. This interpretation may fit with the finding that stimulation of the rostral pole of the SC mainly suppresses ipsilateral saccades, although the suppression occurs on bilateral saccades (Paré and Guittton 1994). It is tacitly assumed that OPNs project bilaterally to EBNs and IBNs, but as yet there is no experimental evidence to support the bilateral inhibition by single OPNs. Instead, we have evidence that single OPNs project to EBN and IBN areas.
mainly on the opposite side (Ohgaki et al. 1987; Strassman et al. 1987). Thus these OPNs may suppress the initiation of ipsiversive saccades if they are activated directly or by the SC by FEF stimulation.

FEF stimulation suppressed only the initiation of Vsacs and Msacs, and not the metrics of the saccades. The stronger suppression of ipsiversive saccades with larger amplitudes suggests that this mechanism may make larger saccades less likely to occur during fixation, but may help generate small catch-up saccades during ipsiversive smooth pursuit eye movements. The stronger suppression of ipsiversive saccades with the more ipsilateral initial eye position suggests that ipsiversive centripetal saccades may occur more easily than ipsiversive centrifugal saccades during fixation. This might contribute to the eye-centering mechanism (Bender 1955). Types of corticofugal neurons that are responsible for FEF suppression of ipsilateral saccades remain uninvestigated. At least 2 groups of neurons so far reported in the FEF might be candidates for FEF suppression: saccade-related neurons and fixation neurons. Smooth pursuit–related neurons might not be responsible for this suppression, since stimulation of the smooth pursuit–related subregion of the FEF evokes ipsiversive smooth pursuit eye movements (MacAvoy et al. 1991). Depending on whether this suppression is related to visual fixation or to reciprocal inhibition for saccade generation, fixation-related output neurons or saccade-related output neurons might be involved for this suppression. A lesion of the FEF in human patients produced an increased frequency of express saccades, especially saccades directed toward the side of the lesion (Braun et al. 1992). In the monkey, FEF inactivation increased the frequency of premature saccades to ipsilateral targets (Dias and Segraves 1999; Sommer and Tehovnik 1997). These findings suggest the impairment of the suppressive function of fixation neurons in the FEF, and that fixation neurons are more likely to be involved in the present FEF-associated ipsilateral suppression. Further studies are required to identify the exact neural mechanisms that underlie the FEF-associated suppression of ipsiversive Vsacs and Msacs.

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