Interaction of the Two Frontal Eye Fields Before Saccade Onset

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Schlag, J., P. Dassonville, and M. Schlag-Rey. Interaction of the two frontal eye fields before saccade onset. *J. Neurophysiol.* 79: 64–72, 1998. A normal environment often contains many objects of interest that compete to attract our gaze. Nevertheless, instead of initiating a flurry of conflicting signals, central populations of oculomotor neurons always seem to agree on the destination of the next saccade. How is such a consensus achieved? In a unit recording and microstimulation study on trained monkeys, we sought to elucidate the mechanism through which saccade-related cells in the frontal eye fields (FEF) avoid issuing competing commands. Presaccadic neuronal activity was recorded in one FEF while stimulating the contralateral FEF with low-intensity currents that evoked saccades. When an eye-movement cell was isolated, we determined: the movement field of the cell, the cell's response to contralateral FEF microstimulation, the cell's response when the evoked saccade was in the preferred direction of the cell (using the collision technique to deviate appropriately the evoked saccade vector), and the cell's response to a stimulation applied during a saccade in the cell's preferred direction, to reveal a possible inhibitory effect. Complete results were obtained for 71 stimulation-recording pairs of FEF sites. The unit responses observed were distributed as follows: 35% of the cells were unaffected, 37% were inhibited, and 20% excited by contralateral stimulation. These response types depended on the *site* of contralateral stimulation and did not vary when saccades were redirected by collision. This invariant excitation or inhibition of cells, seemingly due to hardwired connections, depended on the angular difference between their preferred vector and the vector represented by the cells stimulated. By contrast, 8% of the cells were either activated or inhibited depending on the *vector* of the saccade actually evoked by collision. These results suggest that the consensus between cells of oculomotor structures at the time of saccade initiation is implemented by functional connections such that the cells that command similar movements mutually excite each other while silencing those that would produce conflicting movements. Such a rule would be an effective implementation of a winner-take-all mechanism well suited to prevent conflicts.

INTRODUCTION

Multiplicity of representation is a common feature of the mammalian brain not only in the sensory but also in the motor domain. For the central control of gaze, we know of several forebrain structures, including the frontal eye field (FEF) (Goldberg and Segraves 1989), the supplementary eye field (SEF) (Schlag and Schlag-Rey 1987), and the lateral intraparietal cortex (LIP) (Andersen and Gnadt 1989), which, based on unit recordings and the effects of stimulation, qualify as centers of visuooculomotor processing and possibly as sources of gaze commands. To this list should be added an important subcortical center: the superior colliculus (SC) (Sparks and Hartwich-Young 1989). Each of these structures has its assortment of visual, visuomotor, motor-related, and fixation cells. Because individual studies usually focus on a single structure, the capabilities of this structure tend to be singled out to the point where one could conclude hastily that no other center really is needed for shifting gaze. Yet there are several central oculomotor structures, and if, theoretically, they have the capacity to compete with each other, nevertheless, they always seem to cooperate in producing an eye movement.

What prevents conflicting orders from being simultaneously issued by neurons in the same or separate regions of the brain? Considering the multitude of stimuli in a natural environment, at any moment attention may be solicited in several directions. However, neurophysiological recordings indicate that, when a saccade is imminent, neurons for which the particular direction and amplitude of that saccade is the preferred vector fire concomitantly in all these different structures. All these neurons seem to agree on the timing and destination of the planned eye displacement. How is this consensus achieved? Ideally, to approach this problem, one should find a way to trigger a saccade from one of the structures—thereby leaving no doubt about the site of origin of the saccade—and observe the effects on cells of the same or other structures. In practice, we have used electrical stimulation for probing the effect of one oculomotor center on another, though it is obviously an artificial procedure. In our first study, applying this paradigm (Schlag-Rey et al. 1992) we stimulated one FEF in monkey and recorded the responses of SC saccade-related cells. We found that FEF stimulation excited an SC cell if the vector of the electrically evoked saccade matched the preferred vector of the cell. Otherwise, the stimulation was inhibitory.

We now report on FEF interactions: stimulation was applied in one FEF while recording from contralateral FEF neurons. Each FEF generally is considered to be responsible for directing contraversive movements of both eyes (Bruce and Goldberg 1985; Bruce et al. 1985) although coactivation of FEF neurons in both hemispheres probably is required for performing vertical saccades, up or down. Otherwise, for saccades away from the vertical, one would assume that activations on both sides should be mutually exclusive. Do the FEFs ignore each other, with any potential conflict in command being resolved downstream? Does one FEF take the initiative by turning the other off? If so, is this censorship implemented by inhibiting all cells or only those which would issue a conflicting command? Preliminary results have been presented in an abstract form (Schlag et al. 1996).

METHODS

Under deep pentobarbital sodium anesthesia, a monocular search coil was implanted in two female monkeys (1 *Macaca nemestrina,*

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1 *M. mulatta*) according to the method described by Judge et al. (1980). The leads of the coil were secured to a pedestal of dental cement anchored by screws to the animal's skull. After recovery and a few weeks of training in simple saccade tasks, a second surgery was performed to place symmetrical wells over the arcuate sulcus of both hemispheres.

During both training and recording sessions, the monkey sat in a primate chair with the head immobilized, facing a tangent screen 61° horizontal by 50° vertical at a distance of 132 cm. Visual stimuli were low intensity (25 mc^2), small (0.23° diam) luminous dots produced by a Tektronix 608 oscilloscope and back-projected through a wide-angle lens. The monkey's head was in the center of a magnetic field of 17.7 and 35.4 kHz generated in paired 63-cm diam coils. The animal was rewarded for making a saccade toward a target that could appear at varying locations when the central point of fixation was extinguished (after 200–800 ms of fixation). All experiments were run in complete darkness.

Two microelectrodes were lowered concomitantly in the FEF wells. One was used for stimulation (usually trains of 20 cathodal pulses of 0.2-ms duration at 400 Hz delivered via a Haer isolation unit). The selection of particular sites of stimulation rested on the possibility to evoke saccades with low-intensity currents (usually 20–30 μA and never larger than 50 μA). Saccades were evoked while the animal fixated a point of fixation (square window of $\pm 2°$ around the point of fixation). All evoked saccades were contraversive. Usually, a single site of stimulation was chosen and used throughout a whole session, whereas the recording microelectrode was advanced to study the responses of one to four units successively. Only presaccadic units were selected for this experiment: their activity started to increase before saccade onset in at least one direction. They were either movement or visuomovement cells, discharging in brief sharp bursts or in a more sustained manner. Other types of units, such as visual or fixation-related, were not studied.

For each unit studied, the experimental protocol consisted of a battery of four tests. *Test 1* consisted of mapping the movement field with visual evoked saccades. A precise determination of the cell's ''best vector'' was done by successive approximation using 50-ms flashes positioned with a joystick. When the movement field was large (i.e. maximal responses obtained over a large area), the best vector was considered to be terminating at the center of the movement field. *Test 2* served to determine the cell's response (or lack thereof) to a contralateral FEF stimulation that evoked a saccade from a steady eye position ($\geq$300 ms of steady fixation). *Test 3* served to determine whether the cell's response was altered when the saccade evoked by contralateral stimulation was deviated—by the collision technique (Dassonville et al. 1992; Schlag and Schlag-Rey 1990)—in such a way as to correspond to the cell's preferred vector (i.e., the vector associated with the most intense firing). *Test 4* was complementary to *3*: stimulation was applied during a movement in the cell's preferred direction. Any inhibitory effect thus could be revealed because the cell was activated fully at that time. In *tests 3* and *4,* the direction and amplitude of the initial saccade and the timing of stimulation were manipulated and adjusted by trial and error until the desired vector of the electrically evoked saccade was obtained. Points of fixation and visual stimuli were positioned so that all saccades to be compared throughout the four tests started from approximately the same site in orbital coordinates.

Cell responses were classified as excited, inhibited, or unaffected by inspection of the rasters, histograms, and spike density profiles (spike trains convolved with Gaussian filters, s = 10 ms). No statistical tests were applied to set criteria for distinguishing these types of responses because it was clear that the effects obtained often vary with the intensity of stimulation, which, in most cases, had to be limited to avoid a contamination of the records by shock artifacts. For instance, many cells classified as ''unaffected'' might have been reclassified as ''inhibited'' if larger currents had been used. But it is not sure that such a reclassification would be meaningful because the effect of larger currents is also less circumscribed, the size of the neuronal population directly affected being dependent on the intensity of stimulation. Therefore we decided to report the number of cells in each class as a realistic assessment of the effect of a stimulation just sufficient to induce a saccade. Stimulation intensity was adjusted to the minimum necessary for 95–100% elicitation of saccades.

Measurements of the latency of unit responses were made on individual records. For inhibition, the time of the last spike before interspike interval increase was averaged. For excitation, the time of the first spike after interspike interval decrease was averaged. The averages thus calculated corresponded to the values suggested by histograms (such as in Fig. 2) but with a better resolution. Latencies were calculated only for cases of excitation and inhibition that appeared obvious from visual inspection (see Fig. 5). As noted in the last paragraph, the less obvious cases were classified as ''unaffected'' even though we admit that they could turn to be weak excitations or inhibitions, especially if the stimulation current had been increased.

We did not pursue testing in the few cases where spikes appeared to be time-locked to each pulse of the stimulation train because such spikes actually could be distorted shock artifacts. Therefore it is quite possible that a small number of interesting cases of antidromic invasion or monosynaptic excitation have been discarded systematically because they could be confused erroneously with occurrences of artifacts. We were less interested in antidromic or monosynaptic effects of stimulation than in the activity preceding the saccades and time-locked to their onset.

Histological sections showed electrode tracks located in the rostral bank of the arcuate sulcus. Too many tracks were made to afford individual identification. The FEF region was thoroughly explored from sites representing 2° saccades uniformly to sites representing 34.3° saccades horizontal, up, and down.

RESULTS

Eighty-five FEF presaccadic units were submitted to the four tests, and complete results were gathered for 71 of them (38 movement, 33 visuomovement cells). On this basis, four classes of responses were distinguished.

For 35% of the cells (n = 25), the stimulation had no visible effect on the unit activity. A typical example is provided by the cell illustrated in Fig. 1, which will be used to give a concrete description of our experimental tests. All the rasters from this cell (recorded in the right hemisphere) are aligned on saccade onset (at *time 0* ms).

Test 1

A 50-ms flash was presented while the monkey fixated a central fixation point for a randomly varying time (400–700 ms). The monkey made a saccade to the flash location when the fixation point was turned off. The location of the target was varied in successive trials until the maximal response was obtained. The cell illustrated in Fig. 1 was visuomotor and its preferred vector (drawn within the box labeled A) was L4.5°U6°. By convention, L = left, R = right, U = up, and D = down. In this and all following figures, a line terminating on a circle indicates a visually guided saccade. The raster in Fig. 1*A* shows the cell firing with a movement toward the site of that target flashed at the time indicated by the tick marks. The firing started ~80 ms after stimulus onset and continued throughout the targeting saccade.

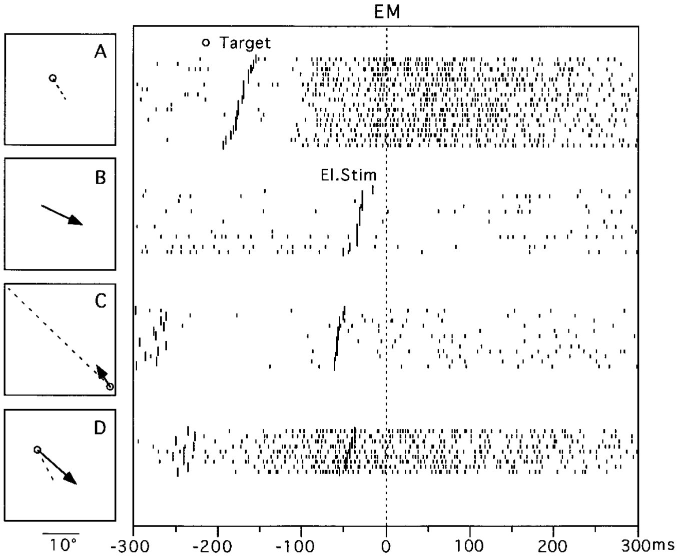

FIG. 1. Unit "unaffected" by contralateral frontal eye field (FEF) stimulation. All rasters are aligned on saccade onset. In this and all following figures containing rasters, the vectors in the boxes indicate *relative* displacements in space: for each cell, they started at approximately the same position in orbit. Visually guided saccades are represented by dotted lines terminating on the target marked by a circle. Electrically evoked saccades are represented by plain lines terminated by an arrowhead. Both types are present in *tests 3* and *4*. *A*: rasters synchronized on the onset of a saccade to a target presented L4.5°U6° in the dark, at time indicated by tick marks. In *B–D,* rasters are synchronized on the onset of the electrically evoked saccade. When there are 2 tick marks, as in *C* and *D,* the first indicates target onset, the second stimulation onset. *B*: fixed-vector saccade (R11.5°D5.5°) evoked by electrical stimulation of contralateral FEF when the eyes were stationary. *C*: deviated saccade (L4°U6°, i.e., similar to the saccade in *A*) evoked by the same stimulation as in *B* but applied during an initial visually guided saccade (R29°D27.5°). Nevertheless, the cell was not activated. *D*: deviated saccade (R11°D10°) evoked by the same stimulation as in *B* applied during an initial visually guided saccade (L5.5°U10°, i.e., in approximately the same direction as *A*). The cell activity was not modified.

Test 2

A saccade was evoked by stimulating the contralateral FEF (left, in this case). Tick marks in Fig. 1*B* (and also in Fig. 1, *C* and *D*) indicate the onset of the train of pulses. In Fig. 1*B* the eyes were stationary when the stimulation was applied. Under this condition the fixed-vector of the electrically evoked saccade was R11.5°D5.5°. In this and all following figures, a line terminated by an arrow represents the vector of an electrically evoked saccade. Here, this vector (*B*) was almost opposite to the preferred vector of the cell (compare vectors in *A* and *B*). The raster *B* shows that the cell did not respond or, perhaps, was slightly inhibited.

Test 3

The saccade evoked by contralateral stimulation (same site as in *test 2*) was made to correspond to the preferred vector of the cell (see raster and box in Fig. 1*A*). The collision paradigm was used to obtain this vector (Schlag and Schlag-Rey 1990). With this paradigm, Dassonville et al. (1992) have shown that one can elicit saccades in any direction and practically of any size from any FEF site. The electrical stimulation has to be applied when the eyes are already moving, for instance, toward a flashed target, and the target location has to be calculated so that the vector of the electrically evoked saccade has the desired metrics (for details, see Dassonville et al. 1992). Thus for instance, the vector evoked by electrical stimulation in Fig. 1*C* was made to match the vector of the visually evoked saccade shown in *A*. To that effect the stimulation was timed automatically to occur 20 ms after the onset of a 40° saccade directed toward a target located left and down. The trajectory of both the visually guided saccade and the electrically evoked saccade are shown in Fig. 1*C.* As much as possible for each cell tested, we tried to have all electrically evoked saccades starting from the same position in orbit to facilitate the comparison of the accompanying neural activity. To meet this requirement, it was sometimes necessary to select an eccentric site as the origin of the electrically evoked saccade, especially if the visually guided saccade had to be large, as in Fig. 1*C.* Note that the site and electrical parameters of stimulation in Fig. 1*C* were exactly the same as in Fig. 1*B.* The objective of this *test 3* was to find out whether the cell would fire when the artificially induced saccade matched the one with which the cell was normally active (i.e., the preferred vector as determined by the *test 1*). As the raster Fig. 1*C* shows, this certainly did not happen in this case.

Test 4 is complementary to 3

Here the objective of the collision paradigm was to activate the cell maximally before electrical stimulation (as seen in Fig. 1*D*) so that, on an elevated background activity, an inhibition caused by stimulation could be revealed. Again, contralateral stimulation was applied while an initial saccade to a target was executed in the cell's preferred direction (up left as shown in Fig. 1*D*). It is clear that, even in this favorable condition, there was no evidence that electrical stimulation of the contralateral FEF inhibited the cell (Fig. 1*D*), despite the fact that a saccade was evoked by stimulation.

Let us stress that what we call "absence of effect" as illustrated in Fig. 1, is not a trivial result since it establishes the fact that the behavior of an FEF neuron during a movement electrically evoked from the contralateral side can be different from that observed when the same movement is naturally evoked, for instance, by a visual stimulus.

Inhibited cells

For 37% of the cells ($n = 26$), the only visible effect of stimulation was an inhibition. Most often, inhibition could not be detected when the cell activity was low, which happened commonly when the eyes were immobile (*test 1*). It could be revealed, however, by timing the stimulation so that it occurred on a background of activation produced by the collision paradigm (see *test 4* described in METHODS). Rasters and histograms of unit activity in *test 4* were compared with those obtained in *test 1* in which no electrical stimulation was applied. Figure 2 presents data from 4 of the 26 inhibited cells. For each of the four, the two rasters show the enhanced activity that accompanies a visually guided saccade in the cell's preferred direction (shown in the boxes placed *opposite* to each raster). The *bottom rasters* are synchronized on the onset of electrical stimulation. The vector of the saccade produced

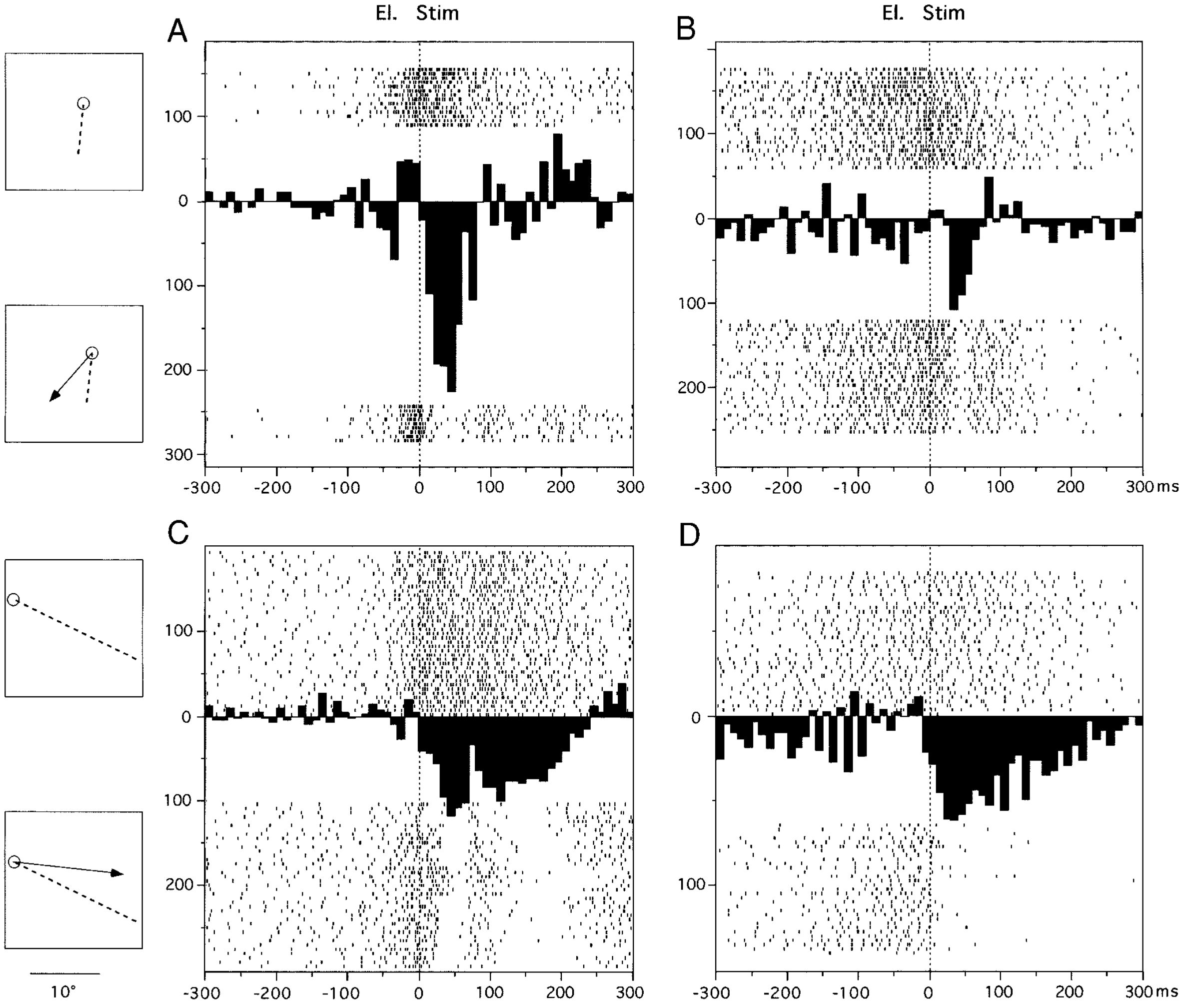

FIG. 2. Inhibitory effect of stimulation revealed on the activation that accompanies a visually guided saccade in the cell's preferred direction. Rasters of 4 different units are synchronized on stimulation onset. However, no current was applied in the trials illustrated by the *top rasters,* which therefore serve as controls. Electrical stimulation applied in the trials illustrated by the *bottom rasters* induced an inhibition. For each cell, the histogram shows the difference (positive and negative) between *bottom* and *top rasters,* with the inhibition caused by the electrical stimulation in the *bottom rasters* appearing as a downward deflection. Vectors of initial visually guided saccades and electrically evoked saccades are shown in boxes next to the respective rasters.

by that stimulation also is shown in the *bottom boxes* of all four cases. Although there was no electrical stimulation in the *top rasters,* a synchronizing pulse was delivered at the time when the stimulating train would have been started. This is a convenient way to provide a time reference for comparing data with and without electrical stimulation. In other words, the difference between the *bottom* and *top rasters* was that the electric current was delivered during the *bottom raster* and turned off during the *top raster.* Inserted between the rasters are difference histograms of the cell activities obtained under these two conditions (stimulation vs. no stimulation), with the inhibition caused by the electrical stimulation in the lower rasters appearing as a downward deflection. The latency of the inhibition was 5–20 ms (shorter in Fig. 2, *A* and *D* than in *B* and *C*), and its duration was 20–50 ms in all but three cases (including *C* and *D* in Fig. 2) in which it lasted much longer. Later we shall compare the latencies of inhibitory and excitatory responses with the latencies of the electrically evoked saccades.

Excited cells

For 20% of the cells ($n = 14$), the invariant effect obtained by contralateral stimulation was a burst of discharges. Among the cells showing such an excitatory response, 10 cells had *ipsiversive* movement fields. The sample of ipsiversive cells collected during these experiments was rather large (18% of the movement cells) but not unusual [for instance, 2 of the 11 corticopontine neurons identified by Segraves (1992) were ipsiversive]. Because, for ipsiversive cells, the laterality of the movement fields was the same as the laterality of the saccades evoked by stimulation of the contralateral hemisphere, it is perhaps not surprising that they were activated by stimulation. There were no ipsiversive cells among the first two types described: unaffected and inhibited cells. Although the other four excited cells were not ipsiversive, their direction preferences were also angularly close to the vector of the electrically evoked saccade (i.e., both upward or both downward).

In Fig. 3 are shown the responses of four of the ipsiver-

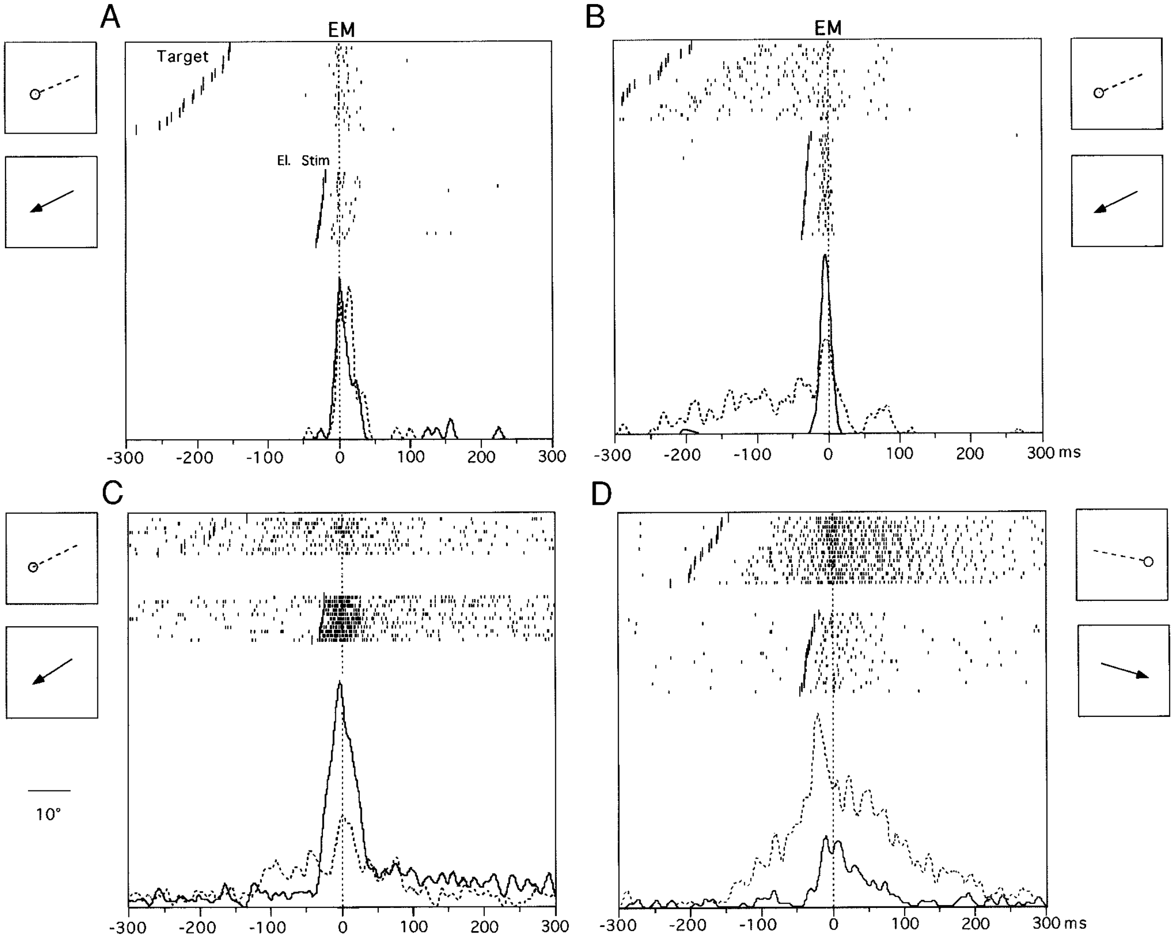

FIG. 3. Saccadic burst activity evoked by electrical stimulation (*bottom rasters*) compared with activity accompanying visually guided saccades (*top rasters*) in 4 ipsiversive FEF units. Rasters are synchronized on saccade onset. Tick marks indicate the target onset (*top raster*) or stimulation onset (*bottom raster*). Saccade vectors are shown in boxes *next* to the rasters. Spike density profiles: · · ·, *top raster;* ——, *bottom raster.*

sive cells to illustrate their variety. The rasters are synchronized on the onset of the saccades, visually guided in *top rasters* and electrically evoked in *bottom rasters* of Fig. 3, *A–D.* In some cases, the temporal characteristics of both types of responses were very similar (short bursts as in *A*). In other cases, of course, the long prelude typical of visuomotor cells responding to visual stimuli was absent in the electrically evoked response (as seen in *B*). Bursts also could be produced by the electrical stimulus even if no eye movements were triggered (Fig. 4). In this case, the stimulus current was adjusted at threshold and saccades were evoked ~50% of the time. Although the stimulation was identical, saccades were evoked in the trials represented by the *top raster* (Fig. 4), no saccades were evoked in the trials represented by the *bottom raster*, but unit responses were the same. This effect was seen in each of the nine ipsiversive cells tested.

In Fig. 5, the average latencies of all inhibitory (squares) and excitatory (circles) invariant responses to electrical stimulation reported above have been plotted against the latency of the evoked saccades. In all but four cases, the changes of firing rate started 10–30 ms before saccade onset. The four exceptions were ipsiversive FEF units in which the movement-related activity was presaccadic when elicited by a visual target but postsaccadic when elicited by contralateral stimulation at the site tested.

The results presented up to now suggest that the inhibitory or excitatory effects of stimulation (57% of the cells) were related unconditionally to the site of stimulation: that effect did not change when the direction of the evoked saccade was modified, even possibly inverted. These results are reminiscent of those obtained in a previous study on the effects of FEF stimulation on SC neurons (Schlag-Rey et al. 1992).

Modulated cells

The last six cells (i.e., 8% of the cells described in this report) were quite different from the others because their excitation or inhibition depended on the actual vector produced by stimulation under the conditions of collision. These cells (4 movement, 2 visuomovement) were excited when the vector of the electrically evoked saccade was made to match the cell's preferred vector, and inhibited otherwise.

Of these six cells, which we call ''modulated'', three had ipsiversive movement fields and three had contraversive fields. In Fig. 6, evoking ipsiversive or contraversive saccades by the same stimulation, we contrast one of these modulated cells (Fig. 6*B*) with one of the invariably excited

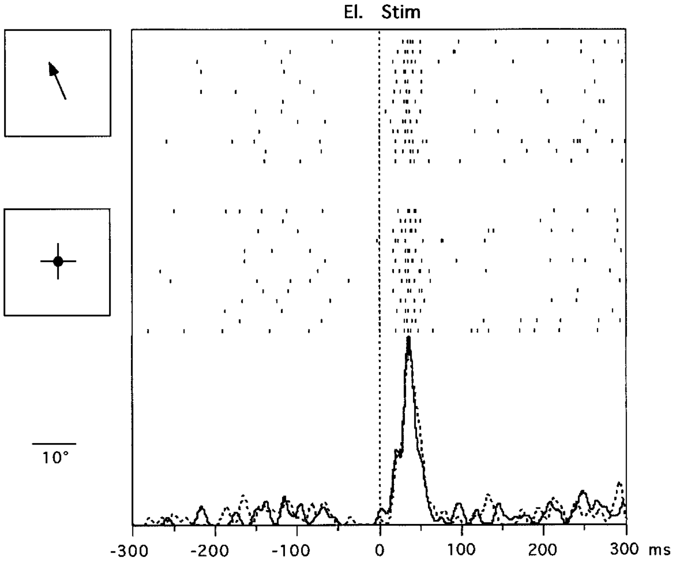

FIG. 4. Excitatory responses to electrical stimulation do not depend on the elicitation of a saccade. All rasters are from the same cell; stimulation was near threshold. Rasters are synchronized on stimulation onset. *Top raster*: activity when a saccade was evoked. *Bottom raster*: when no saccade was evoked. Spike density profiles correspond to *top raster* (——) and *bottom raster* (· · ·).

type (Fig. 6*A*), described above. This illustrates the difference between cells that always responded in the same way to the stimulation, whatever the orientation of the movement induced and those that reflected the orientation of that movement.

The cell in Fig. 7 shows the continuous variety of responses from excitation to inhibition, which justifies the label ''modulated.'' This cell had a preference for visually guided right-down saccades (*raster A*). After a weak excitation, it was inhibited by a stimulation that induced upward saccades if applied when the eyes were steady (see *raster* and *vector C*). In *rasters B* and *D–F*, the responses vary as the direction of the evoked vector was modified by collision.

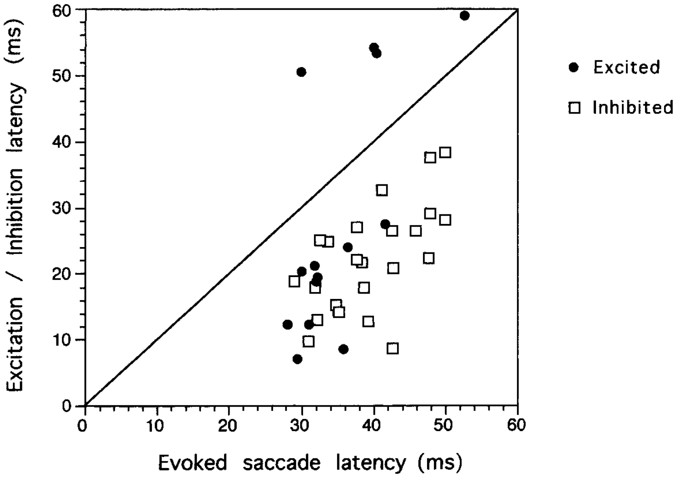

FIG. 5. Latencies of excitatory and inhibitory responses to contralateral electrical stimulation as a function of latencies of saccades evoked by that stimulation.

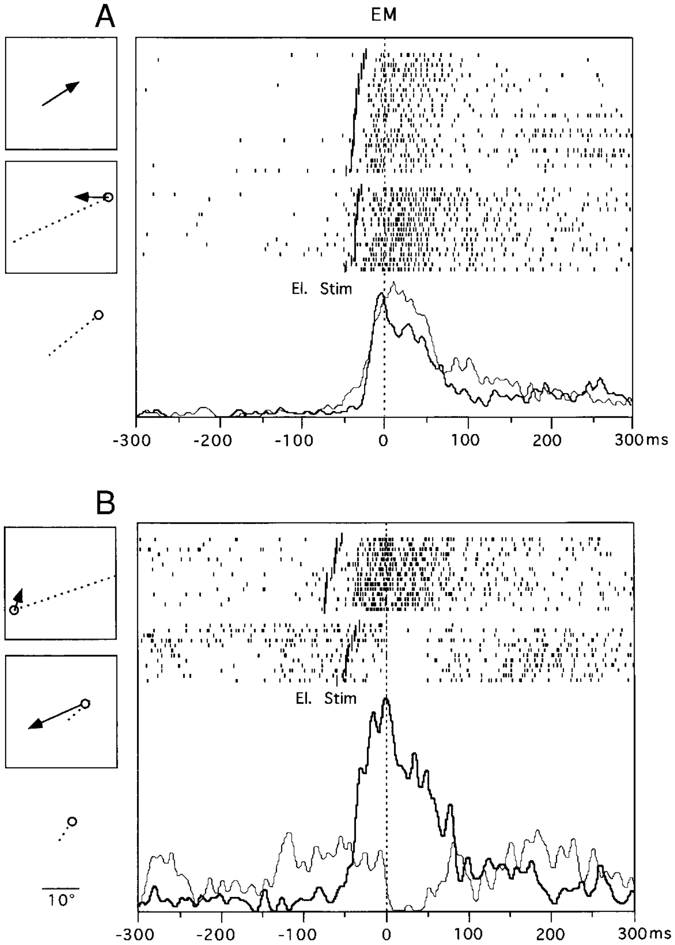

FIG. 6. Contrast between 2 modes of responding to electrical stimulation. Cell in *A* always responded by a burst whatever the direction of the saccade evoked from the tested site, whereas the cell in *B* responded as a function of the direction of the evoked saccade. Rasters are synchronized on the onset of the evoked saccade. Tick marks indicate stimulation onset. Spike density profiles correspond to *top rasters* (thick lines) and *bottom rasters* (thin lines). Best saccade vectors are indicated (dashed lines) at *bottom left* for each cell (no raster, no spike density curve).

Finally, we related the different effects of stimulation reported here to the relative similarity or disparity of saccade vectors represented at the FEF sites of recording and stimulation. Figure 8*A* provides the result of this analysis in terms of angular difference between the vectors (abscissa) and the ratio of their amplitude (ordinate). In this mode of presentation, the data pertaining to each recorded cell are represented by a point, although it should rather be a ''patch'' proportional to the size of the movement field. The larger the distance of a point (patch) from the origin (amplitude ratio of 1 at 0°), the greater is the vector disparity and the less frequently were excited cells encountered. In Fig. 8*B*, only the angular difference is taken in consideration, and the data are pooled in three groups of increasing disparity. Of the cells falling in the category with the lowest angular difference (<40°), 70% were excited. The largest group (44%) in the next category (40–120°) were the inhibited cells. In the final category (>120°), 47% of the cells were unaffected by stimulation. The three histograms show a definite trend: the probability of finding excited cells decreases, whereas the probability of finding unaffected and inhibited cells increases with angular difference. Modulated cells were distributed equally in all three categories.

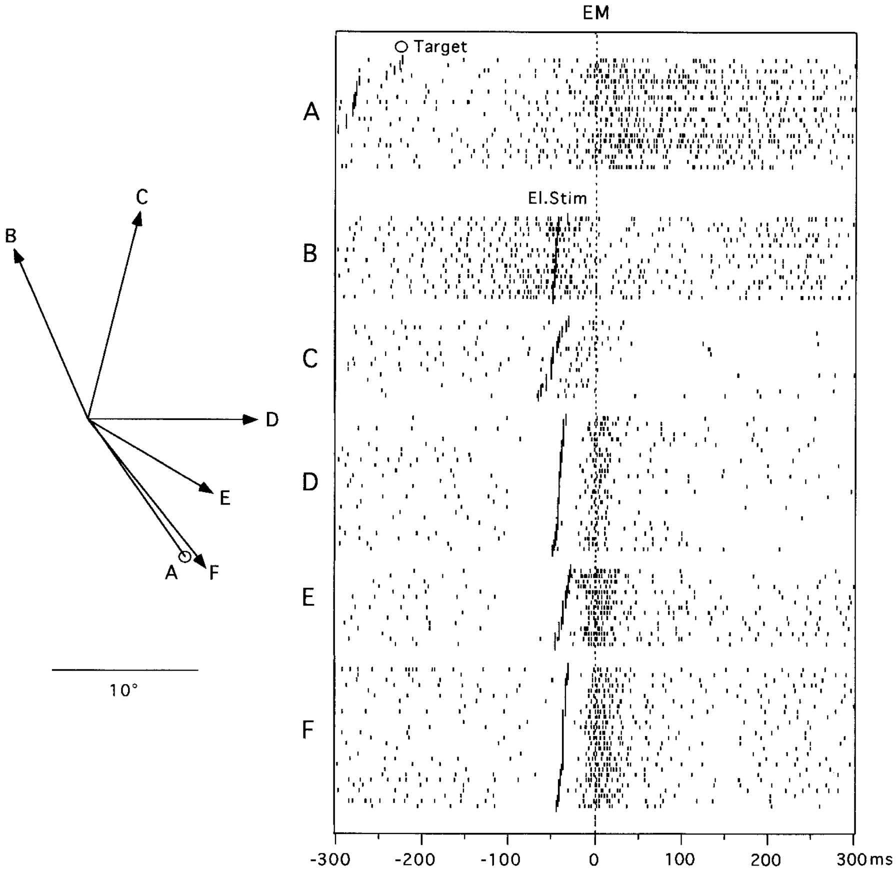

FIG. 7. Modulated cell: variations of response as a function of the direction of the evoked saccade. Rasters are synchronized on saccade onset. In *A*, the saccade is directed to a visual target. Tick marks indicate target onset. In *B–F*, saccades are electrically evoked from a single FEF site. Tick marks indicate stimulation onset. Collision was used in all these cases except in *C* where the eyes were steady when the stimulation was applied. Initial saccades in collision trials are not shown. *Rasters A–F* correspond to the evoked movements *A–F* shown at *left.*

DISCUSSION

In a recent study of visual search, Schall and Hanes (1993) have shown that, if a distractor stimulus is placed within the response field of an FEF visuomotor cell, the cell's response is inhibited on trials in which an accompanying target stimulus is placed near—but not within—the response field. This is evidence that a search task involves dynamic interactions beyond the local FEF cells directly activated by a stimulus. Schall and Hanes postulated a mechanism of central facilitation and surround inhibition to explain target selection. We think that the effects observed in the present study, using electrical stimulation instead of visual targets, represent another type of interaction, probably occurring at a processing stage later than target selection. Indeed, the neural activity evoked by electrical stimulation serves to initiate the saccade, but the successful execution of this command depends on silencing all opposing neural commands. This is an interpretation of the unit responses we have observed in the contralateral hemisphere. Very likely, inhibitory effects also would be detectable in the population of ipsilateral FEF neurons the preferred vectors of which differ from that of the evoked saccade; however, the technical limitations of simultaneously recording and stimulating in the same FEF make verification of this idea difficult.

There are not many paths through which the interhemispheric effects of stimulation observed in this study could have been obtained. The most plausible is the corpus callosum. The existence of mutual connections between the FEFs has been established (e.g., Gould et al. 1986; Pandya and Vignolo 1971). Two possibilities of callosal transmission should be considered: either orthodromic callosal excitation, leading to spreading excitatory and inhibitory effects via interneurons, or antidromic callosal invasion, leading to the same effects via recurrent collaterals and probably also interneurons. The present data do not allow us to differentiate these possibilities because we systematically discarded the cases of short latency responses following at high frequency (see METHODS). Beside the corpus callosum, it seems that any FEF-to-FEF pathway would have to relay through the brain stem, at the level of the superior colliculus or the pontine tegmentum. However, regardless of the path involved, it remains that functional relations between FEF neurons are not haphazard but are instead organized on the basis of saccade vectors. Thus if a cell's preferred vector corresponds to the vector of the saccade evoked from the contralateral side, one can predict that it will be excited by that stimulation.

From the results of this study, one can attempt to build an overview of the distribution of activity within the neuronal population of the FEF when a saccade is produced. First, a large proportion of cells—those for which the saccade direction is not the preferred one—are silenced by stimulation. This is a fact that observations of activity during evoked saccades could not reveal clearly without the help of collision because, when the eyes are immobile, the firing of FEF neurons is usually too low to reveal an inhibition. But, with the help of collision, we learned that many neurons of the nonstimulated FEF were actively silenced. Proportionally, they were numerous, about as numerous as the cells that did

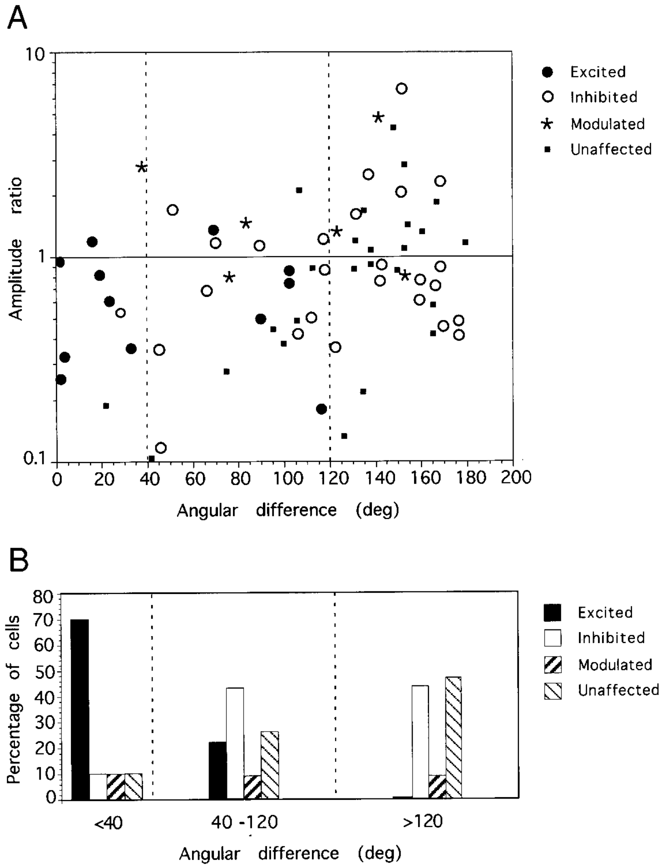

FIG. 8. *A*: distribution of cell types (excited, inhibited, modulated, and unaffected) as a function of the angular difference between the paired (evoked and preferred) saccade vectors (abscissa) and their amplitude ratio (ordinate). Ordinate scale is logarithmic. *B*: histograms of the same data showing the percentage of each type within 3 ranges of angular difference.

not change their activity. This suggests an involvement of the ipsilateral FEF. Blocking the opposition is a simple way to implement a winner-take-all mechanism by preventing antagonistic commands from being issued concurrently. Presumably, a number of FEF cells, not only on the nonstimulated side but also on the stimulated side, are similarly inhibited if their preferred vector is different from the chosen vector of the initiated saccade. We have seen that the same principle rules functional relations between FEF and SC (Schlag-Rey et al. 1992) and in fact may be universal. We can thus imagine a ''consensus network'' interconnecting oculomotor centers.

We do not know which cells in the population studied were FEF output cells sending commands to the SC or to the brain stem tegmentum. It is not excluded that some of the ipsiversive cells in the ''excited'' group were among them because Segraves (1992) was able to find some ipsiversive corticopontine neurons that he identified by antidromic collision. Besides, contralateral corticotectal connections have been demonstrated (Distel and Fries 1982; Shook et al. 1990). Such a crossed projection would be easily understandable if the corticotectal neurons were ipsiversive or if their preferred vector was close to the vertical. There is evidence that hemispherectomized patients can generate voluntary saccades directed contralaterally to the excised hemisphere (Troost et al. 1972). On the other hand, it is also possible that few or none of the neurons that were excited by contralateral stimulation projected down to the brain stem. These excited cells could be interneurons, and, if they were inhibitory, they could well be on the callosal path responsible for inhibiting contralateral FEF cells.

The fact that excited FEF cells were activated even if the electrically evoked movement was not actually produced (Fig. 4) or even if the opposite movement was elicited by collision (Fig. 6) indicates that this activation was due to the stimulation and not secondarily to a feedback from movement execution.

It has been suggested that one of the functions of callosal connections between the two FEFs is to ensure the necessary cooperation of both sites for generating vertical saccades (Bruce and Goldman-Rakic 1984). In our study, the combined orientation of the two FEF vectors was not often favorable for testing this hypothesis. In fact, only rarely did we see a transhemispheric excitatory effect related to a vertical saccade. More and different data (e.g., simultaneous recordings from the 2 FEFs) are needed to substantiate the theory. However, our results indicate that bilateral cooperation in the generation of vertical saccades is not the only role—and probably not even the main one—of excitatory callosal connections.

It has been shown that saccades electrically evoked from any FEF site can be deviated in any direction—and even inverted—by the collision paradigm (Dassonville et al. 1992). One hypothesis assumes that the correction of the trajectory occurs at the level of the FEF or before, such that the emerging command, at that stage, is already spatially accurate. Originally, this notion of saccade accuracy was applied to describe results obtained with the double-step paradigm (Goldberg and Bruce 1990), but it could be extended to explain collision data also. According to this hypothesis, if the saccade correction involves a left-right inversion, the executed command should come from the FEF opposite to the site of stimulation. Were the inverted saccades observed here produced from the side contralateral to the electrical stimulation? In principle, our results indicate that this is possible because some FEF cells (i.e., the modulated cells) became active when the actual saccade vector was inverted so that its termination fell in the cell's movement field. One thus can argue that the proper signal may become available from the appropriate FEF site. However, only 6 cells were found showing this particular behavior out of 71 saccadic cells studied. Theoretically, if spatial accuracy depends on the FEF output, the deviated trajectory of the evoked saccade should be determined by the modulated cells that were the ones firing according to the executed saccade vector. However, we found that such cells represented only 8% of the cells studied, whereas 55% emitted an incorrect signal (i.e., that would be driving the eyes in a different direction) and 37% remained silent even though the saccade vector might terminate in their movement field. It does not seem likely that all or nearly all output FEF neurons were among the 8% of the cells of the modulated type because the works of Segraves and Goldberg (1987) and Segraves (1992) have shown that FEF movement cells provide the largest group (~50%) of corticotectal and corticopontine neurons. Among the nonmodulated, 34 were movement cells. Thus it is doubtful that the correcting mechanism responsible for redirecting the course of a saccade by collision could be located at the level of the FEF or upstream from it.

In conclusion, our results raise new issues and call attention to interactions among oculomotor neurons, especially those located in opposite hemispheres, at the time of saccade initiation.

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