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The frontal eye field provides the goal of saccadic eye movement

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Summary. Microstimulation of oculomotor regions in primate cortex normally evokes saccadic eye movements of stereotypic directions and amplitudes. The fixed-vector nature of the evoked movements is compatible with the creation of either an artificial retinal or motor error signal. However, when microstimulation is applied during an ongoing natural saccade, the starting eye position of the evoked movement differs from the eye position at stimulation onset (due to the latency of the evoked saccade). An analysis of the effect of this eye position discrepancy on the trajectory of the eventual evoked saccade can clarify the oculomotor role of the structure stimulated. The *colliding saccade paradigm* of microstimulation was used in the present study to investigate the type of signals conveyed by visual, visuomovement, and movement unit activities in the primate frontal eye field. Colliding saccades elicited from all sites were found to compensate for the portion of the initial movement occurring between stimulation and evoked movement onset, plus a portion of the initial movement occurring *before* stimulation. This finding suggests that activity in the frontal eye field encodes a retinotopic goal that is converted by a downstream structure into the vector of the eventual saccade.

Key words: Eye movements – Electrical stimulation – Frontal eye field – Spatial coordinates – Oculomotor command – Monkey

Introduction

Stimulation, single unit, anatomical, and lesion studies have clearly demonstrated that the primate frontal eye field (FEF) plays some role in saccade generation and guidance (see Goldberg and Segraves 1989 for a review). But what exactly is this role? Although the FEF output signal is often assumed to encode the movement vector of the upcoming saccade, this view is not necessarily correct. It is possible that the FEF output encodes, instead, a retinotopic goal that must be converted, in some downstream structure, into the final saccade vector. How can these two hypotheses be distinguished? The usual strategy has been to record from single units while a monkey is performing an oculomotor task, using double-step stimulus presentations, in which the vector of the retinal error differs from that of the saccade vector required for an accurate response (i.e. the oculomotor system must compensate for the first movement when programming the second). In the oculomotor areas tested in this way thus far, cells exhibiting presaccadic movement, visuomovement, or visual activity seem to register the saccade vector rather than the retinal error (superior colliculus (SC), Mays and Sparks 1980; lateral intraparietal area, Gnadt and Andersen 1988; FEF, Goldberg and Bruce 1990). These results could be interpreted to mean that each of these areas performs the same calculation, sending a motor error to the brainstem oculomotor generator independently of the others. It is possible, though, that one structure is generating this error and sending (in a feedforward or feedbackward manner) a signal to the other areas, conscripting them into its service.

Electrical stimulation provides another way of distinguishing between a retinotopic goal or motor error output signal, without ambiguity concerning the location from which the signal initiating the saccade has arisen (i.e. the microstimulation site). Stimulation in most oculomotor regions, when the eyes are stationary, will evoke a saccade of a direction and amplitude stereotypic of the electrode site (Fig. 1A); the fixed-vector nature of these movements is compatible with the creation of either a retinotopic goal or a motor error signal. To distinguish between the two, one must alter the position of the eye between the time of stimulation onset (when, presumably, the error signal is created) and the occurrence of the evoked movement. This is accomplished by applying the stimulation train during an ongoing natural saccade (Fig. 1B). The latent period of

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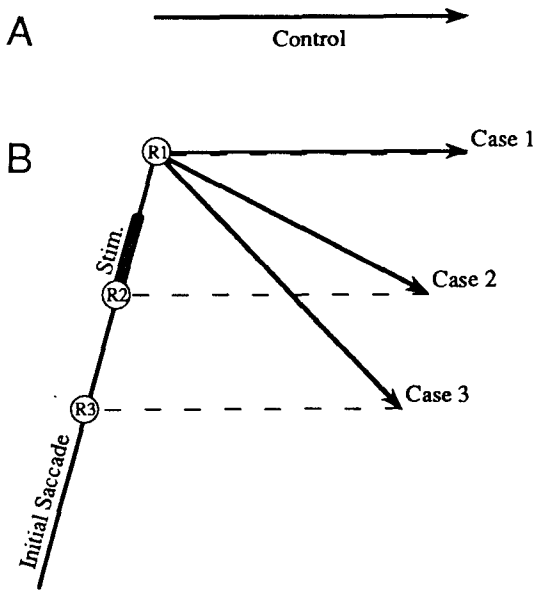

Fig. 1A, B. Schematic description of the colliding saccade paradigm. **A** Stereotypic fixed-vector saccade (control) evoked while the eyes are steady. **B** Possible outcomes when stimulation (shaded bar) is applied during an initial natural saccade. Case 1: evoked movement (arrow) in same direction as fixed-vector control (noncompensation hypothesis); mean control vector (dashed lines) plotted from the end of the evoked movement yields a reference eye position (R1) at initial movement offset. Case 2: evoked movement compensates for the portion of the initial movement occurring after stimulation onset (efferent-compensation hypothesis), having a reference position (R2) at stimulation onset. Case 3: evoked movement compensates for a portion of the initial movement before and after stimulation onset (afferent-compensation hypothesis), having a reference position (R3) before stimulation onset

the evoked saccade allows the initial movement to continue before the evoked movement begins. This is the essence of the colliding saccade paradigm (Schlag and Schlag-Rey 1987a; Schlag-Rey et al. 1989; Schlag et al. 1989), used in the present study to investigate the nature of the FEF output signal.

What are the possible outcomes of applying the colliding saccade paradigm to test an oculomotor structure? If stimulation were to create an artificial motor error signal, specifying the actual movement vector, the trajectory of the evoked movement, beginning after the latent period, should be unaffected by the intervening saccade (*noncompensation hypothesis*, case 1 in Fig. 1B). Noncompensatory evoked movements are seen with stimulation of the deep layers of the superior colliculus (SC), where presaccadic movement activity is found (Schlag-Rey et al. 1989). On the other hand, if stimulation were to create an artificial retinotopic goal defined with respect to the eye position at stimulation onset, the evoked movement should compensate for any change of eye position that occurs during the latent period (*efferent-compensation hypothesis*, case 2 in Fig. 1B). This type of efferent-compensatory movement is found with stimulation of the superficial layers of SC where cells exhibit visual responses (Schlag-Rey et al. 1989). SC sites of visuomovement activity are of two types: the more superficial cells produce efferent-compensatory saccades; deeper ones, noncompensatory. Yet a third finding would be expected if stimulation were to create an artificial retinotopic goal with reference to an eye position *before* stimulation onset – the evoked saccade should compensate for all of the initial movement occurring after stimulation onset as well as a portion of the movement occurring before (*afferent-compensation hypothesis*, case 3 in Fig. 1B). This type of afferent-compensatory movement, evoked from the internal medullary laminar complex (IMLc) of the thalamus (Schlag et al. 1989), is expected when stimulating a site located before the oculomotor programming stage that is responsible for compensation of intervening eye movements.

Because of the seemingly parallel functions of SC and FEF (Schiller et al. 1980), one could hypothesize that FEF units showing visual responses mediate retinotopic goals as do units in superficial layers of SC, while FEF cells exhibiting presaccadic movement responses mediate motor error signals as in deep layers of SC. Stimulation at sites associated with visual activity, therefore, should evoke efferent-compensatory colliding saccades (case 2 in Fig. 1B), and sites associated with movement activity should produce noncompensatory saccades (case 1). An alternative hypothesis, considering the tight functional bond between thalamus and cortex, is that FEF mechanisms of saccade generation are more similar to those of IMLc, where activity mediates a retinotopic goal with reference to an earlier eye position (case 3). Schlag and Schlag-Rey (1987a) found compensation at the 4 FEF sites they tested, but the amount of compensation was neither quantified nor compared across sites with different unit response types.

In this investigation, we found that stimulation of every FEF site, regardless of the type of unit activity present, elicited afferent-compensatory colliding saccades. It follows that the unit activity in FEF represents a retinotopic goal with reference to an earlier eye position. This goal is later converted, by a downstream structure, into a motor error. Brief descriptions of partial results from this study were presented elsewhere (Dassonville et al. 1989; Schlag and Schlag-Rey 1990).

Methods

During an initial surgery, a monocular search coil (Robinson 1963) was implanted in each of two female adult monkeys (*Macaca nemestrina*, monkey Z, and *Macaca mulatta*, monkey W) according to the method described by Judge et al. (1980). Wire leads from 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, a second surgery was performed to place a recording well over the arcuate sulcus. Animals were under deep sodium pentobarbital anesthesia during all surgical procedures.

During both training and recording sessions, the monkey sat in a primate chair with the head immobilized; a tangent screen 61° horizontal by 50° vertical was placed 132 cm in front of the eyes. Visual stimuli were low intensity (15 mcd/m^2), small (0.23° diameter) luminous dots back-projected onto the tangent screen by a Tektronix 608 oscilloscope equipped with a wide-angle projection lens. Magnetic fields of 40 and 80 KHz (created by sinusoidal currents flowing through paired vertical and horizontal coils (63-cm diameter)

positioned around the animal's head) generated, in the search coil, the signal used to measure eye position.

For this investigation, the monkeys were taught three main tasks. The first of these simply required the monkey to orient its gaze toward the location of a visual stimulus; reinforcement with fruit juice was contingent on maintaining fixation for at least 500 ms in a small window (4°) surrounding the target. Each of the remaining tasks used two visual stimuli – the first a fixation point, the second a saccade target. In the immediate saccade task, the offset of the fixation point was synchronous with the onset of the target. After reorienting the gaze toward the target location, the monkey was rewarded as described above. In the delayed saccade task (Hikosaka and Wurtz 1983), the target stimulus was briefly presented during the fixation interval so that the fixation point remained present for 500 ms after the offset of the target. The monkey was required to maintain its gaze on the fixation point until its offset, and then to make a saccade to the remembered location of the target to receive the juice reward. The size of the reinforcement window was increased to 6° in the delayed saccade task to offset the upward bias of saccades directed to remembered locations (Gnadt et al. 1991). If the gaze moved before the offset of the fixation point, the trial was aborted. Because the dim fixation point and target could appear at any time and at any location on the screen with no prior warning, the monkey searched continuously. While most sessions were performed in complete darkness, a dim red background light was occasionally used to decrease the slow ocular drift common in complete darkness. At the end of each session, which typically lasted 1–4 h, the animal was returned to its home cage. Since the monkeys were very willing to work for the juice reward, neither food nor water deprivation was required.

During the recording sessions, tungsten microelectrodes were lowered into the FEF through the recording well. The same microelectrodes were used for single unit recordings and microstimulation. Unit recordings were used to determine each isolated neuron's response type (visual, visuomovement, movement, postsaccadic, etc.), as well as its receptive or movement field. The delayed saccade task was used, as needed, to temporally separate the occurrences of the flash and the subsequent targeting saccade, allowing a distinction to be made in the type of unit activity observed. Microstimulation was performed with trains of 10–20 cathodal pulses of 0.2-ms duration at 400 Hz from a Haer constant-current stimulator. Current stability was verified by measuring the voltage drop across a 1-kohm resistor in series with the preparation. To prevent excessive tissue damage, current values never exceeded 40 μA; at a majority of stimulation sites (89/98), current values were kept under 20 μA. Animals were observed continuously with a video camera (an infra-red lamp provided ambient light); no skeletal or facial movements were ever evoked by the electrical stimulus.

Electrical stimuli were either triggered manually by the experimenter or automatically delivered at delays of 0–500 ms after online saccade detection. Preliminary analysis showed that the effects of collision (as measured by a compensatory deviation of the evoked movement) were no longer evident 200–300 ms after an intervening movement. Therefore, trials in which a spontaneous or visually-evoked movement preceded the stimulation train by less than 200 ms were considered colliding trials in subsequent analyses; trials in which the eyes were stationary during the 300-ms period preceding stimulation onset were considered controls. To avoid confusion between those trials that were colliding and those that were controls, we excluded from analysis any trial having an intervening saccade beginning more than 200 ms, but less than 300 ms, before stimulation onset. Only sites yielding fixed-vector control saccades were analyzed ($n=98$); sites yielding control saccades with a scatter of more than 10° in either the horizontal or vertical amplitude were excluded ($n=16$). This tended to eliminate many of the sites from which large (>20°) movements were evoked.

Eye and target position, unit activity, and microstimulation signals were digitally sampled (1 KHz) on-line. Occasionally, the signals were recorded onto an Ampex PR280 analog tape recorder and were later replayed and digitally sampled. For the analysis of the effects of collision, 500-Hz digital plots of the control and colliding saccades were obtained from a Hewlett-Packard 7475A plotter.

At the conclusion of the study in monkey Z, coagulation marks were made at sites of interest in the FEF by passing a direct current (−2.5 μA for 5 s) through the stimulating electrode. The animal was subsequently injected intravenously with a lethal dose of sodium pentobarbital and perfused with a formalin solution. The brain was blocked in situ, sectioned at 60 μm, and stained with thionine for histological analysis of electrode placement. All sites analyzed with the colliding saccade paradigm were localized in the anterior banks of the left and right arcuate sulci.

Monkey W is currently undergoing further oculomotor testing; verification of electrode placement, therefore, was accomplished using purely physiological methods: 1) the various types of unit activity present were similar to those described by Bruce and Goldberg (1985), with receptive and movement fields moving closer to central vision as the electrode penetrations were moved laterally; 2) microstimulation evoked saccades, with thresholds as low as 5 μA, toward the receptive or movement field of the cell present at the stimulation site (Bruce et al. 1985); and 3) cortical topology, as determined by electrode depth, suggested the presence of the arcuate sulcus just posterior to the sites tested. Given these three types of information, we can state with confidence that the sites tested were within the arcuate FEF as described by Bruce and Goldberg (1985).

Results

The colliding saccade paradigm was used to test 98 FEF sites (67 from left FEF and 21 from right FEF of monkey Z, 10 from left FEF of monkey W). At 66 of these sites, single units were isolated and their responses investigated before the microstimulation trials were begun: 56 had some type of task-related activity; 10 had activities uncorrelated with any aspect of the task. At the remaining 32 sites, no units were isolated. Sites of task-related activity were further divided into groups (Bruce and Goldberg 1985) having visual ($n=8$), visuomovement ($n=28$), movement ($n=9$), postsaccadic ($n=7$), or eye position related activities ($n=4$). This information allowed us to compare the colliding saccade results across the sites having different activity types.

As in Schlag et al. (1989) and Schlag-Rey et al. (1989), we assumed that microstimulation created an artificial error signal (either retinal or motor) possessing the angle and amplitude of the fixed-vector control movements; the mean vector of these controls was used to represent the error signal created with stimulation at each site. To quantify the existence and amount of compensation present in each colliding saccade trial, the mean control vector was plotted from the endpoint of the compensatory evoked saccade, yielding an estimation of the eye position to which the error signal was referenced (*reference position*). A reference position (R1 in Fig. 1B) falling at the offset of the initial movement (and, therefore, at the onset of the evoked movement) would be indicative of motor error creation (noncompensatory, case 1); one falling along the trajectory of the initial movement (R2 or R3) would be indicative of retinal error creation (efferent- or afferent-compensatory, cases 2 and 3, respectively).

The remainder of the Results section is broken into three parts. The first of these provides a general description of the colliding saccade paradigm as it relates to our findings with FEF microstimulation. The second part of

this section documents, in greater detail, the existence or absence of compensatory-evoked movements from each of the sites tested with the colliding saccade paradigm. As stated in the Introduction, this determination should allow us to differentiate between sites carrying a motor error signal (i.e. having noncompensatory evoked movements) and those specifying a retinotopic goal (i.e. having efferent- or afferent-compensatory movements). The third part of this section is an attempt to quantify the amount of compensation in order to differentiate between retinal error sites using a reference eye position concurrent with stimulation onset (efferent-compensatory) and those using a reference eye position before stimulation onset (afferent-compensatory).

General description of FEF colliding saccades

Figure 2A illustrates the typical results observed when the colliding saccade paradigm was applied to the FEF. Starting soon after initial movement onset, electrical stimulation (onsets denoted by tick marks) evoked movements whose *trajectories* were unlike those of fixed-vector controls evoked from the same site, but whose *endpoints* were similar (termination field of the fixed-vector controls is denoted by the polygon). Thus, the direction and amplitude of each colliding movement was altered to compensate for the previous displacement, allowing the movement to reach its goal despite starting from an eye position different from that at stimulation onset.

The amount of compensation present for each trial, based on the location of the reference position along the trajectory of the initial movement, was found to depend on the timing of microstimulation. Stimulation trains that began shortly after (0–30 ms) initial movement onset evoked saccades that compensated for most of the intervening eye displacement. At the other end of the continuum, trains beginning well after (> 300 ms) the onset of the initial movement evoked saccades that were unaffected by the presence of the initial movement (i.e. they were again fixed-vector). Trains with intermediate delays evoked movements that compensated for only a portion of the initial movement. This dependency on timing is consistent with the results of Schlag et al. (1989) using thalamic IMLc stimulation.

Because of the compensatory nature of the colliding saccades, the trajectories of the evoked movements greatly depended on the timing and trajectories of the initial movements. By choosing appropriate microstimulation onset delays, as well as initial movement directions and amplitudes, it was possible to evoke movements in almost any given direction and amplitude from a single stimulation site (Fig. 2B). In particular, compensatory movements could have amplitudes larger (or smaller) than the fixed-vector controls (1 in Fig. 2B), or directions opposite the

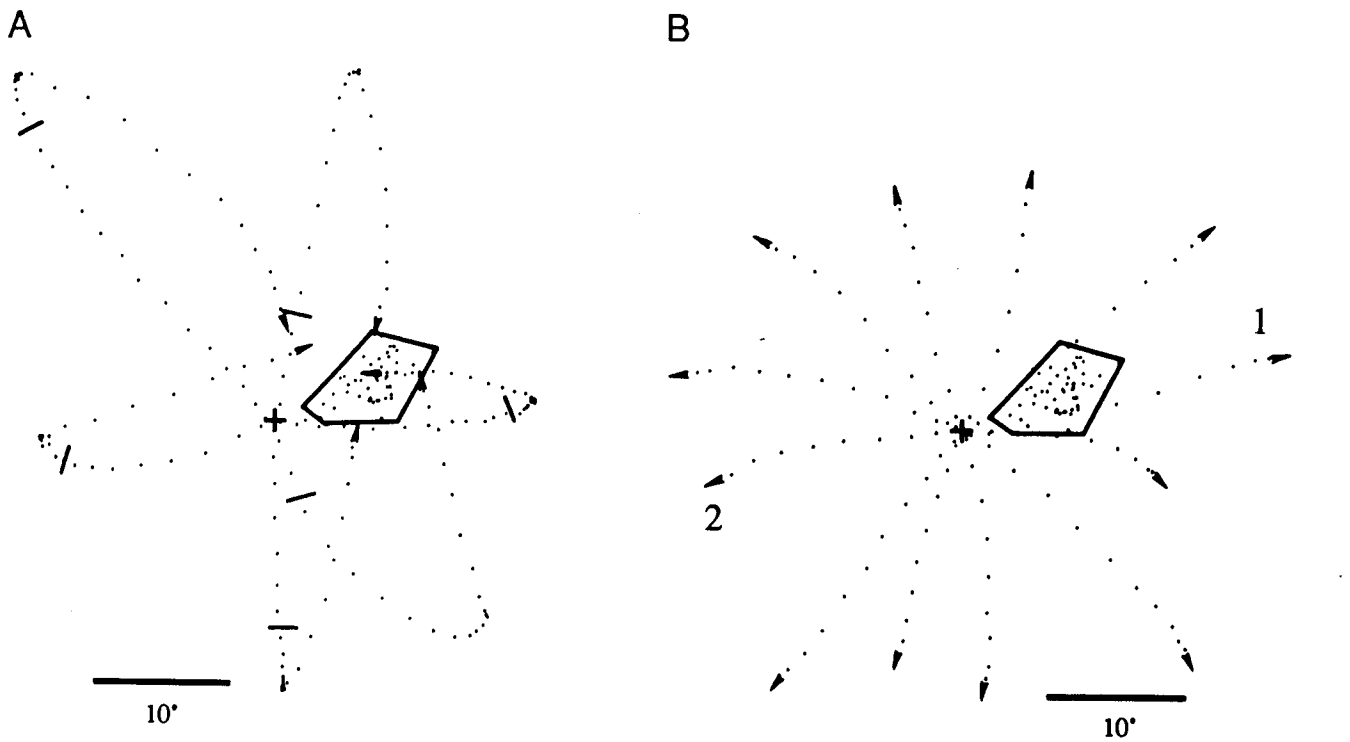

Fig. 2. **A** Typical compensatory saccades evoked by FEF stimulation (11 μA) from a site of presaccadic movement unit activity. Polygon encloses termination field of fixed-vector controls. Each trajectory shows the initial movement (cross = superimposed onsets) as well as the compensatory evoked saccade. Tick marks = stimulation train onsets. **B** Further examples of compensatory movements evoked from the same site as in **A**. Origin (cross) now denotes evoked movement onset (initial movements not shown). Note the variety of directions and amplitudes achieved, including amplitudes larger than the fixed-vector controls (1), and directions opposite the controls (2). Sampling rate = 250 Hz

controls (*reversals*, 2 in Fig. 2B). Reversals of the horizontal and/or vertical components could be easily and consistently evoked from most sites of stimulation. Most noteworthy are the horizontal reversals, which demonstrate the surprising fact that *ipsiversive* movements can be evoked from sites where contraversive fixed-vector controls are the norm (Fig. 3).

At occasional sites, microstimulation failed to evoke any saccades during collision trials, even though the level of stimulation current was well above (generally 2x) that necessary to evoke the fixed-vector controls. Sites such as these were not investigated in any great detail, and are not included in the population of sites examined below. Alternatively, we often found that it was possible to evoke colliding movements using a current smaller than that necessary to consistently evoke fixed-vector controls. At these sites, it was usually possible to increase the stimulation current to a level adequate to evoke both colliding and control saccades. These, therefore, are included in the population of sites examined below.

For trials in which the stimulation train was applied early during the course of the initial movement, the effect of stimulation was occasionally one of abruptly stopping, or breaking, the initial movement short of its goal *without* evoking a subsequent colliding saccade. This phenomenon of early breaking was more often noticed when the initial movement was visually-evoked rather than spontaneous, but this could possibly be explained by the problems inherent in knowing when a spontaneous movement was "scheduled" to end. At many sites, stimulation was found to break movements in only a subset of the initial-movement directions tested, with compensatory saccades evoked during movements in other directions. More testing is needed to fully understand the direction and timing aspects of this phenomenon.

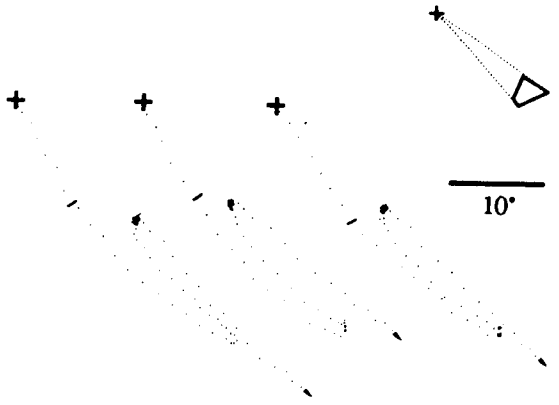

Fig. 3. *Ipsiversive* compensatory movements (reversals) evoked by FEF stimulation (11 μA at a site of visuomovement unit activity) during visually-evoked saccades. Note the resumption of the targeting movement after a short delay, typically seen with colliding saccades evoked from FEF. Polygon encloses termination field of fixed-vector controls. Crosses = onsets of visually-evoked initial saccades, and of fixed-vector controls; tick marks = stimulation train onsets; sampling rate = 333 Hz

Stimulation of all FEF sites yield compensatory saccades

Figure 4 shows the histogram of unit activity (A) from a typical site of visual activity in response to a flash presented into the cell's receptive field, as well as the termination field of the fixed-vector controls (B) and three examples of colliding saccades (C) evoked from the same site. Similar examples of unit activity and colliding saccades are shown in Figs. 5 and 6 for sites of visuomovement and movement activities, respectively. While clear signs of compensation can be seen for each of these three sites of microstimulation, we felt it necessary to inquire whether compensatory saccades could be evoked from every site tested.

Over the course of initial experimentation, it became obvious that the most efficient and obvious demonstration of compensation was the ability to easily evoke colliding

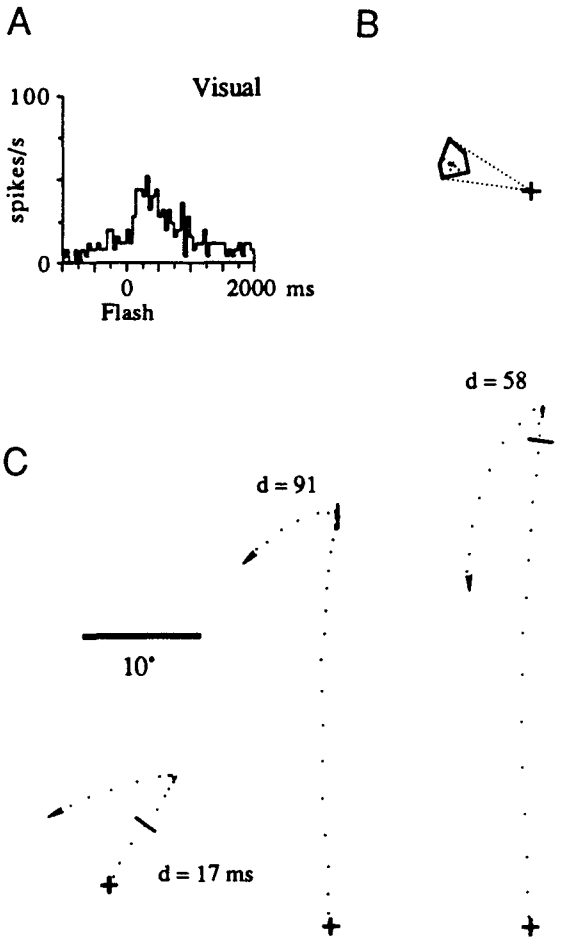

Fig. 4A–C. Compensatory saccades evoked from site of visual unit activity. **A** Peristimulus histogram of unit activity in response to flash (300-ms duration) presented in receptive field. **B** Cross and polygon denote the onset and termination field, respectively, of the fixed-vector controls evoked from this site (10 μA). **C** Examples of colliding saccades evoked from the same site. Crosses = onsets of visually-evoked initial saccades; tick marks = stimulation onset; d = delay (ms) between onset of initial movement and onset of microstimulation; sampling rate = 250 Hz

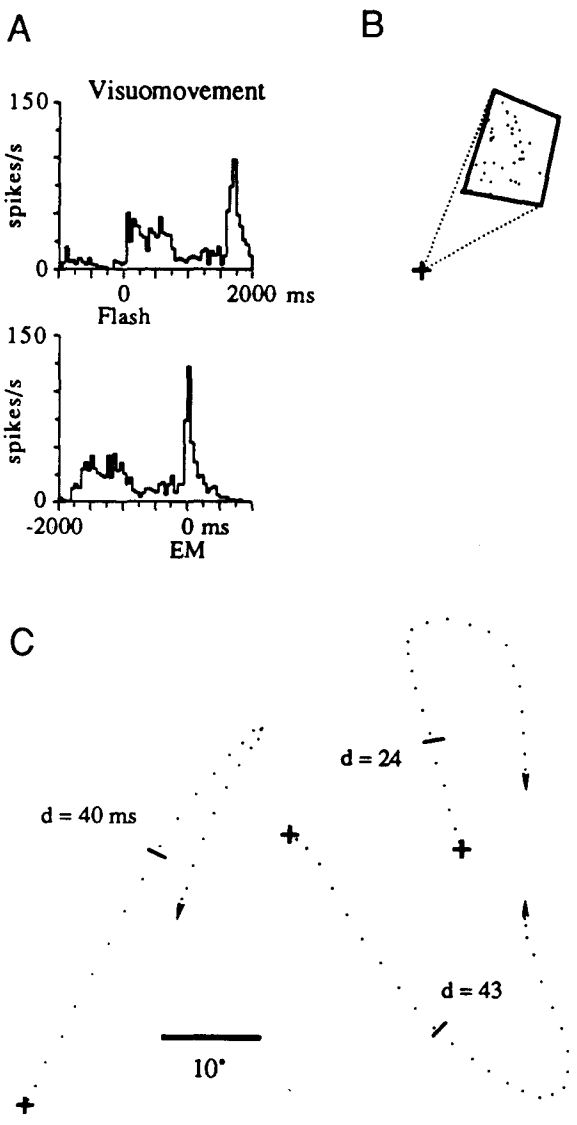

Fig. 5A–C. Compensatory saccades evoked from site of presaccadic visuomovement unit activity. A Peristimulus (upper) and perisaccade (lower) histograms of unit activity in response to flash (500-ms duration) presented in receptive field and subsequent targeting saccade, respectively. B Termination field of the fixed-vector saccades evoked from this site (8 μA). C Examples of colliding saccades evoked from the same site. Same annotations as in Fig. 4

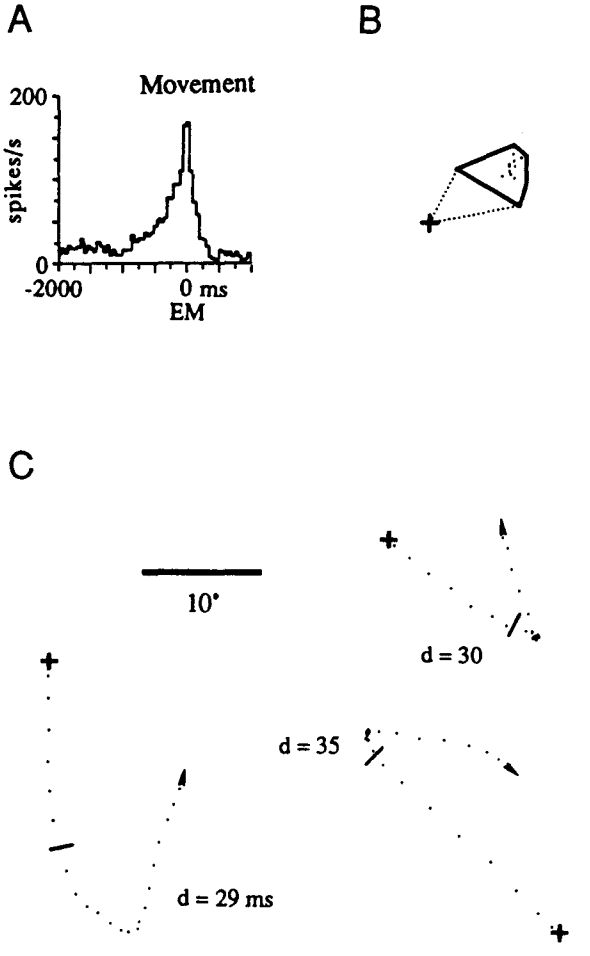

Fig. 6A–C. Compensatory saccades evoked from site of presaccadic movement unit activity. A Perisaccade histogram of unit activity in response to a saccade toward the cell's movement field. B Termination field of the fixed-vector saccades evoked from this site (5 μA). C Examples of colliding saccades evoked from the same site. Same annotations as in Fig. 4

saccades whose directions deviated by more than 90° from those of the fixed-vector controls. At some sites, therefore, the collision tests were implemented to maximize the occurrence of such large deviations (i.e. by applying microstimulation at an optimal delay after the onset of a visually-evoked movement of optimal amplitude and direction). This strategy for recognizing a site as compensatory required fewer trials and thus minimized the possible damage caused by repeated electrical stimulation. Choosing 90° as the criterion of minimal deviation ensured that either horizontal or vertical reversals, or both, were easily evoked from each site classified as compensatory. Of course, the deviation was also inspected for each trial to verify that it was in the proper direction to compensate for the initial saccade. Almost all of the sites tested ($n=82$ from monkey Z, $n=9$ from monkey W) were classified as compensatory in this manner.

At the 7 sites where the criterion of at least 90° of deviation was not specifically sought or was not easily achieved, clear signs of compensation were seen nevertheless. As a method of verifying the occurrence of compensation at these sites, the directions of the saccades evoked on collision trials were statistically compared, with the Mardia-Watson-Wheeler test (Batschelet 1981), to those of the fixed-vector controls. Again, the direction of deviation for each trial was verified to be in the proper direction to compensate for the initial saccade. At each of these 7 sites, the colliding saccades had directions significantly different from those of the fixed-vector controls ($p<0.001$ at 6 sites, $p<0.01$ at 1 site). In summary, compensatory saccades were evoked from all 98 sites tested in FEF, regardless of the type of unit activity present.

Efferent- or afferent-compensation

With the presence of compensation verified at all stimulation sites, a second question arises concerning the extent of compensation associated with the colliding saccades evoked from various stimulation sites: are the evoked saccades efferent-compensatory (as in case 2, Fig. 1) or afferent-compensatory (as in case 3)? The non- and efferent-compensatory hypotheses (which are based on reference positions *at* initial saccade offset and *at* stimulation onset, respectively) allow for precise predictions of colliding saccade trajectories, simply by plotting the mean control vector from the eye positions at initial movement offset and stimulation onset, respectively (Fig. 7, schematic diagrams on the left). However, the afferent-compensation hypothesis (which is based on a reference position located *somewhere before* stimulation onset) allows for no such precision. But if one compares the trajectory of individual trials to those predicted by the non- and efferent-compensation hypotheses, it is possible to determine where the reference position falls in relation to stimulation onset and initial movement offset. In this way, an answer can be found to the question concerning the extent of compensation. To this end, the trajectory of each colliding saccade was compared to the trajectories predicted by the noncompensatory and by the efferent-compensatory hypotheses.

The fit of each hypothesis was evaluated in two ways: 1) linear distance between observed and predicted endpoint locations (upper portion of Fig. 7, with distance measured along the axis of the initial movement – orthogonal deviations were ignored), and 2) angular difference between observed and predicted trajectories (lower portion of Fig. 7). These two measurements were used (rather than either alone) because neither is perfectly reliable: the conclusions to which they lead for a given trial may, indeed, be different, due to under- or overshooting of the evoked saccade. The two measurements were in disagreement in 14.1% of the 672 trials analyzed.

Individual trials were categorized into one of four groups. Each trial having an endpoint (or angle) such that the reference position fell *beyond* the end of the initial saccade was placed into category *a* (theoretically, these types of trials should not occur, but can be expected due to a random scattering about one of the predicted trajectories). Categories *b* and *c* contained trials with reference positions that fell *between* microstimulation onset and the end of the initial saccade – those trials with the reference positions closer to initial movement offset were placed into category *b*, whereas those with reference positions closer to stimulation onset were placed into category *c*. Category *d* represented those trials having reference positions that fell somewhere along the trajectory of the initial movement *before* stimulation onset. In the bar graphs of Fig. 7 (right), the length of each lettered bar depicts the percentage of trials contained within the appropriate category.

With the schema described above, the shape of each bar graph can be used to determine the hypothesis that most closely matches the colliding saccade data. For example, the majority of colliding saccades evoked by stimulation of the deep layers of SC (previously shown to yield noncompensatory saccades, Schlag-Rey et al. 1989), would fall into categories *a* and *b* (since the evoked saccade endpoints would fall close to, but be randomly distributed about, that predicted by the noncompensatory hypothesis). Microstimulation of superficial layers of SC, which yields efferent-compensatory saccades (Schlag et al. 1989), would produce trials evenly divided between categories *c* and *d*. Finally, the data from a stimulation site yielding afferent-compensatory saccades (such as thalamic IMLc, Schlag et al. 1989) would be confined primarily to category *d*.

With microstimulation applied very early after initial movement onset, there is little or no difference in the movements predicted by the efferent- and afferent-compensation hypotheses. Since the purpose of constructing the bar graphs was to make possible a distinction between the two hypotheses, we excluded from analysis those trials in which stimulation onset occurred less than 20 ms after initial movement onset.

The bar graphs in Fig. 7 allow a comparison of the data from sites of visual (A), visuomovement (B), and movement (C) unit activities, and in each the majority of the trials clearly fall into category *d* – closely conforming to the afferent-compensation hypothesis. Indeed, of the 181 trials taken from 5 typical sites of visual activity (Fig. 7A), 84.0% fall into category *d* in both distance and direction measurements, whereas 3.9% fall into a combined group of categories *a*, *b*, and *c* in both measurements (12.1% were ambiguous, having conflicting results in the two measurements). In Fig. 7B, 77.1% of the 175 trials (taken from 5 typical sites of visuomovement activity) fall into category *d* in both graphs; 3.5% fall into categories *a*, *b*, or *c* (19.4% ambiguous). Because the most revealing aspect of the present study concerns the nature of the FEF output signal, we felt it necessary to closely analyze the colliding saccade results from each of the 9 sites where pure movement activity had been recorded. Figure 7C contains the bar graphs from these sites, with 86.7% of the 316 trials falling into category *d* and 0.9% falling into categories *a*, *b*, or *c* (12.4% ambiguous). Furthermore, at none of these 9 sites were the results less conclusive than 75.0% in category *d* and 6.3% in categories *a*, *b*, or *c* (18.7% ambiguous). In summary, afferent-compensatory saccades were evoked from each FEF site examined, regardless of the type of unit activity present.

Discussion

Role of FEF in saccade goal formation

By comparing the trajectory of a colliding saccade with the trajectories of the fixed-vector control movements evoked from the same site, one can determine the type of signal represented by the unit activity at that site (i.e. motor error, retinotopic goal, etc.; Schlag-Rey et al. 1989; Schlag et al. 1989). An evoked movement that does not compensate for any portion of the initial saccade supports the hypothesis of motor error creation. A compensatory evoked movement, on the other hand, is consistent with the

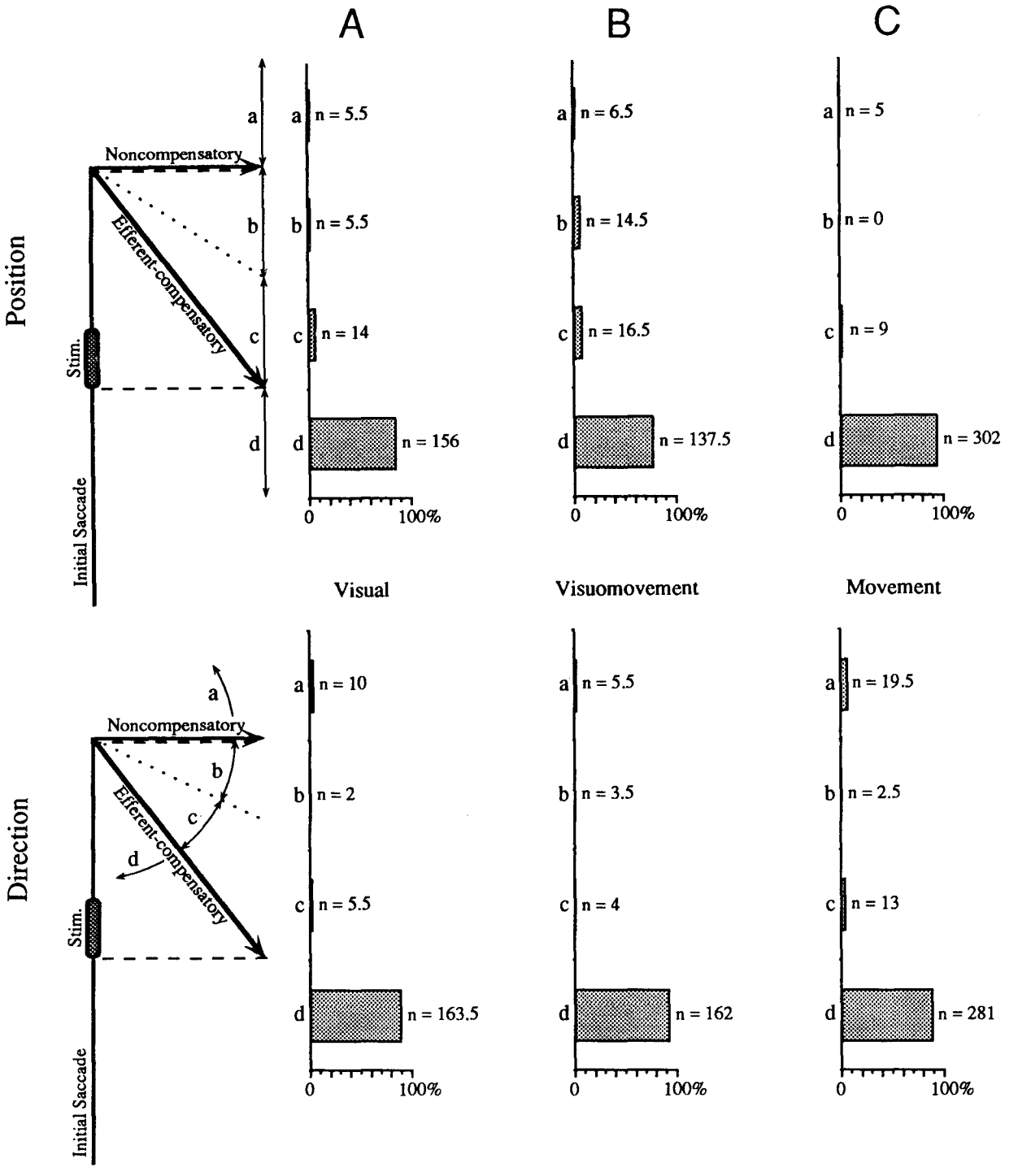

Fig. 7A–C. Bar graphs demonstrating the extent of compensation found in FEF colliding saccades. Schematic diagrams of colliding saccade trials (left) depict the predicted trajectories of the non-compensatory and efferent-compensatory hypotheses, found by plotting the mean control vector (dashed lines) from the end of the initial saccade and the onset of microstimulation (shaded bar), respectively. This schema was used to categorize each trial into groups *a*, *b*, *c* or *d*: trials with evoked saccades having endpoints (lettered arrows in upper diagram depict the endpoint range for each category) or directions (lettered arrows in lower diagram) such that *a*) the reference positions fell beyond the end of the initial saccade; *b*) the reference positions fell after stimulation onset, but closer to the end of the initial saccade than to stimulation onset; *c*) the reference positions fell after stimulation onset, but closer to stimulation onset than to the end of the initial saccade; and *d*) the reference positions fell before stimulation onset. Dotted line depicts the division between categories *b* and *c*. **A** Bar graphs show the percentage of trials falling into each of the 4 categories, evoked from 5 typical sites of pre-saccadic visual unit activity. *n* = number of trials in each category; trials that fell exactly between 2 categories were split and placed into both categories – hence the presence of fractions. **B** Similar graphs showing data from 5 typical sites of visuomovement unit activity. **C** Similar graphs showing data from all 9 sites of movement unit activity. High percentage of trials in category *d* supports the afferent-compensation hypothesis for each of the unit activity types

creation of a retinotopic goal; an additional analysis – quantifying the amount of compensation present – is necessary to determine the eye position used as a reference for this goal.

With compensation found at every site tested, FEF unit activity does seem to encode the retinotopic goal of the eventual saccade. In this way, FEF is much more similar to superficial SC or thalamic IMLc than to deep SC. Compensatory movements were evoked even from sites having pure movement unit activities. Since cells at these sites form the largest group of projections from FEF to SC (Segraves and Goldberg 1987), it seems that the output of the FEF encodes this retinotopic goal, not a motor error signal. This is in agreement with the results of Segraves et al. (1990), who, while recording from FEF presaccadic neurons, found no consistent relationship between spike density and motor error.

The second question addressed by the present study concerned the amount of the initial movement compensated for by the electrically-evoked movement. From the answer to this question, one can infer the relative location of FEF among the series of stages necessary for saccade goal formation. Figure 7 shows that, as in thalamic IMLc, saccades evoked from all FEF sites compensated for even a portion of the initial movement occurring before microstimulation onset. Again, it is important to note that this was true even at sites of movement activity. Thus, it seems that FEF is located early in the process of saccade programming, *before* the stage of compensation for intervening movements.

The conclusion that FEF is located before the stage of compensation appears incompatible with the model of FEF function proposed by Goldberg and Bruce (1990), who suggested that FEF *is* the site of compensation, and that FEF output encodes a desired saccade vector with respect to the current eye position. Goldberg and Bruce developed this vector subtraction model on the basis of single unit recordings in FEF while monkeys made saccades to double-step stimuli. Their findings show that the responses of units having movement-related activities are more closely correlated with the actual saccade vector than with the retinotopic goal created by the second step, as are the responses of most (but not all) units having visual and visuomovement responses. These findings led Goldberg and Bruce to suggest that units having movement-related activities lie downstream from the site of compensation, whereas units of visual activity were of two populations: a majority downstream from the site of compensation and a minority upstream. Predictions based on this model would lead one to expect mixed results when applying the colliding saccade paradigm to FEF: microstimulation of only a small portion of visual activity sites would yield afferent-compensatory evoked movements as were seen in the present study, whereas stimulation of movement activity sites (as well as most visual and visuomovement activity sites) would evoke movements compensating for only the portion of the initial movement occurring after stimulation onset (as is seen in superficial SC). The latter prediction was not upheld in the present study. Thus, there is an incompatibility between the conclusions drawn from FEF single unit and microstimulation studies. Some possible explanations for the discrepancy are discussed below.

As stated in the Introduction, one of the advantages of using microstimulation to investigate the function of an oculomotor structure is the ability to pinpoint the origin of the unit activity responsible for evoking a saccade. This is true at one scale – we know that the evoked movements were elicited from the location of microstimulation – but at a smaller scale, this assumption breaks down. It is obvious that microstimulation of a given site affects more cells than just the single cell from which we recorded. For example, stimulation of a site of pure movement activity does undoubtedly excite neighboring cells, whose unit activities are not necessarily – and are probably not – purely related to movement. Knowing this, it could be conjectured that, even when stimulating the FEF output cells (Segraves and Goldberg 1987), the activities produced in neighboring cells might undergo compensation within FEF. However, if we assume that the chance of exciting all FEF cell types is equal, one could expect that the effect of stimulation would be strongest in the output cells and that this direct activation would preempt the indirect effect of the cells whose projections remain local. This conclusion would only be in doubt if, for any reason, the stimulation was never able to directly excite the FEF output cells, but it is difficult to believe that the output cells were never excited at any of the 9 microstimulation sites where pure movement activity was recorded, nor at any of the 5 sites of visuomovement activity. Further evidence that uncompensated unit activity leaves FEF has been obtained by recording from SC single units while applying the colliding saccade paradigm to FEF. A recent study has shown that SC cells, with movement fields similar to that of the stimulated FEF cell, are excited by FEF microstimulation, even if the directions and amplitudes of the evoked movements are altered through the use of the colliding saccade paradigm (Schlag-Rey et al. 1990). SC cells, with movement fields different from that of the stimulated FEF cell, are inhibited by FEF microstimulation, regardless of the trajectory of the compensatory evoked movement (Schlag-Rey et al. 1990; Keller et al. 1990).

Another possible explanation for the discrepancy between the results of unit recording and stimulation studies lies in a recent finding from this laboratory (Dassonville et al. 1991). Normal human subjects were tested on their ability to direct saccades to the location of a brief flash presented around the time of an intervening saccade. Under these conditions, it is known that the oculomotor system mislocalizes the egocentric position of the flash (Honda 1990; Dassonville et al. 1990a and in press). We found, however, that the oculomotor system is capable of using available exocentric (allocentric) location cues to reduce this error (Dassonville et al. 1991; see also Hayhoe et al. 1990 for another example of the oculomotor system's use of exocentric cues). Is it possible that the FEF unit activity recorded by Goldberg and Bruce (1990) occurred in relation to a saccade based on the exocentric relationship of the two stimuli in the double-step task? Perhaps the guidance of saccades based on exocentric cues occurs at a level above the FEF, whereas corrections involving egocentric cues occur at a level below FEF. These explana-

tions for the discrepancy between stimulation and unit response must be investigated further.

Further implications

Using the assumption that the oculomotor system has access to an accurate representation of eye position or displacement (Hallett and Lightstone 1976), Schlag et al. (1989) reasoned that, to avoid localization errors, a delayed version of the eye position signal must be used in the retinal-to-spatial conversion. In their study of thalamic IMLc, Schlag et al. (1989) estimated the duration of this delay to be 46 ms. However, much variability was seen to exist between trials – the estimate for each trial was dependent on the magnitude of the initial saccade-stimulation interval. This dependency was also seen in the present study using FEF stimulation. An explanation for this was proposed by Dassonville et al. (1990b) in light of recent studies questioning the accuracy of the internal representation of eye position (Honda 1990; Dassonville et al. 1990a and in press). These studies have shown that the oculomotor system does not use an accurate representation of eye position for the retinal-to-spatial conversion as Hallett and Lightstone (1976) had concluded, but instead uses a damped, or sluggish, representation. This could account for the colliding saccade paradigm's dependency on the initial saccade-stimulation interval. Further investigations of the damped representation of eye position are in progress, using the colliding saccade paradigm as well as behavioral studies of normal human subjects.

The phenomenon of early breaking of the initial movement at some stimulation sites leads to the prediction of an FEF excitation of brain stem omnipause neurons. Burman and Bruce (1990) have also demonstrated the ability to suppress or delay the onset of visually-evoked saccades with stimulation of certain sites in FEF. A direct pathway from FEF to nucleus raphe interpositus has been described (Stanton et al. 1988), and direct microstimulation of the omnipause neurons has been shown to interrupt an ongoing saccade (King and Fuchs 1977) in a manner similar to that seen with FEF stimulation. Raybourn and Keller (1977) found that microstimulation of deep SC layers caused a brief burst of excitation in omnipause neurons, followed by an inhibition during which any evoked movements may take place. Similarly, with colliding saccades evoked by FEF stimulation, a brief excitation of omnipause neurons may account for the abandonment of the initial movement; a subsequent inhibition of omnipause cells may trigger the onset of the evoked saccade. Perhaps this inhibition is somehow precluded in those trials showing only an early breaking of the initial movement.

The threshold current for eye movements evoked from FEF is lower than in all other cortical regions, with the possible exception of a discrete region in the supplementary eye field, where it may be as low (Schlag and Schlag-Rey 1987b). In addition, latencies of these electrically-elicited saccades are lower than those elicited in other cortical structures. Thus, it is generally assumed that the FEF is the cortical region closest to the final common pathway of saccade generation. Because FEF movement activity does not seem to represent a motor error, probably no cortical location does so. The various cortical oculomotor areas are most likely involved in determining a saccade goal, which is then transformed into a motor error by the subcortical oculomotor regions.

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