Intracortical Microstimulation of Bilateral Frontal Eye Field

NAOTAKA FUJII, 1 HAJIME MUSHIAKE, 1,2 AND JUN TANJI 1

1 Department of Physiology, Tohoku University School of Medicine, Sendai 980; and 2 Precursory Research Organization for Embryonic Science and Technology, JST, Japan

Fujii, Naotaka, Hajime Mushiake, and Jun Tanji. Intracortical microstimulation of bilateral frontal eye field. J. Neurophysiol. 79: 2240–2244, 1998. We trained two monkeys to perform a fixation task. Intracortical microstimulation (ICMS) was applied to the monkey frontal eye field (FEF) while monkeys were fixating on one of five fixation LEDs. The ICMS was applied in two different manners. Under the single stimulation condition, ICMS was delivered to either right or left FEF. Under the paired stimulation condition, bilateral FEF were successively stimulated with an interval of 30–250 ms. The single stimulation elicited contraversive saccades. As reported previously, these saccades were not much affected by initial eye positions, maintaining the same vector. In contrast, the paired stimulation elicited double-step saccades. The first of the paired stimulation elicited constant vector saccades, but the second of the paired stimulation evoked saccades whose vector varied greatly depending on the eye position at the start of individual saccades. The second saccades, starting from various initial positions, were directed to the endpoint of saccades that were elicited from the same FEF site under the single stimulation condition. Endpoints of second saccades varied little despite variations of intervals of the stimulation pairs, ranging from 60 to 150 ms. On the basis of these observations, we propose a novel view that the FEF is involved in directing saccades to an internally referenced visual target.

RESULTS

We analyzed effects of ICMS at 98 stimulation sites within the FEF. When either the right or left FEF was stimulated alone, saccades were evoked toward a direction contralateral to the stimulation sites. Two examples of such single saccades (S1), evoked from the right and left FEF are shown in Fig. 1C. As reported previously (Russo and Bruce 1993), the direction and amplitude of saccades were primarily determined by cortical sites of stimulation and did not vary greatly depending on gaze positions (corresponding to the fixation point in this study). Saccade vectors of S1 evoked from five different fixation points are shown in Fig. 2A.

What kind of saccades would be evoked when both right and left FEF are activated, one after another, with a paired stimulation? If we assume that the FEF stimulation evokes fixed-vector saccades to each component of the paired stimulation, then a double-step saccade would be evoked as if two saccades of two vectors observed in the right and left S1 were evoked in succession. If stimulation of the left FEF is followed by stimulation of the right FEF with a delay, then the double-step saccade may appear as shown in the left panel of Fig. 1D. If the stimulation order is reversed, then the evoked saccades may appear as in the right panel. In both cases, the first (D1) and second (D2) components of the double-step saccades would correspond to the S1 evoked from either the left or right FEF. However, actual saccades evoked by the paired stimulation were not what the fixed-vector hypothesis predicted. Although the first component, D1, appeared not different from the S1 evoked from the same site, the vector of the second component D2 was different from the vector of single saccades. As shown in Fig. 1E, right, the vector of D2 evoked from the left FEF differed from the vector of S1 evoked from the same (left)
stimulation site (interrupted arrow, Fig. 1E). In fact, the D2 appeared as if to be directed toward the endpoint of S1 started from the fixation point (see also the left panel that shows the outcome of left-right stimulation).

To observe whether or not the D2 was directed toward an endpoint of S1 from a fixation point, movement vectors of three sets of D2 initiated from different eye positions are superimposed in Fig. 2C. All vectors shown in Fig. 2C are of saccades evoked from a single stimulation site in the left FEF. While the monkey was fixating a central fixation target (○), stimulation of three different sites in the right FEF (3 sets of D1, not shown) drove the eyes to three different positions. Immediately thereafter, stimulation of a single site in the left FEF evoked saccades with vectors labeled D2, D2′, and D2″. All vectors appeared to be directed toward an endpoint of S1, which was the saccade evoked from the same cortical site when the eyes were fixated on the central fixation point. These observations seem to indicate that the different sets of D2 initiated from multiple eye positions converge on a target of S1. To quantify the degree of convergence, a regression analysis was made according to a method recently reported (Russo and Bruce 1993). In Fig. 2D, left, horizontal sizes of evoked saccades shown in Fig. 2C are plotted against relative values of horizontal eye positions (from the fixation point) at the start of each saccade. In Fig. 2D, right, vertical sizes (upward is positive and downward is negative) are plotted against the relative vertical positions. In both plots, the effects of orbital positions on sizes of evoked saccades appeared large. The regression coefficients calculated from the horizontal and vertical plots were −0.72 and −0.8, indicating strong convergence of the saccades. In contrast, when the single saccades (e.g., 5 sets of S1 shown in Fig. 2A) evoked from different fixation points were similarly plotted (Fig. 2B), the effect of the initial eye position on the saccade size was small. In an example shown in Fig. 2A, horizontal and verti-
FIG. 2. A: examples of saccade vectors (–) evoked by single stimulation of left FEF while monkey is fixating on 5 different points (∗1 started from 5 positions). C: examples of D2 evoked from a single stimulation site in left FEF. While monkey was fixating on a single fixation point, stimulation of 3 different sites in right FEF drove eyes to 3 different positions (arrows labeled D2, D2', and D2") from which 3 groups of saccades evoked by left FEF stimulation initiated. All of D2, D2', and D2" are directed toward an endpoint of S1 evoked from FP. C: horizontal (left) and vertical (right) sizes of saccades evoked by single stimulation (S1) are plotted against horizontal and vertical initial positions of saccades, respectively. Data are obtained from an example shown in A. Positive and negative values of vertical sizes mean upward and downward directions of saccades. Initial eye positions are expressed as relative positions to right (positive values) and left (negative values) of center of central fixation point. Linear regression analysis was made to obtain a regression line and a regression coefficient \( R \) from each data set. According to a linear regression model (Russo and Bruce 1993), size of evoked saccades \( E(p) \) is expressed as \( E(p) = Ec / (R_1 p) \), where \( Ec \) is constant saccade vector for each stimulation site, \( p \) is initial eye position and \( R \) is regression coefficient. If vector of evoked saccade is not affected by initial eye position (fixed vector), then \( R \) is close to zero and \( E(p) = Ec \). On other hand, if evoked saccades converge on a point (converging vector), then \( E(p) / p = Ec \) and \( R \) is close to \(-1\). D: horizontal (left) and vertical (right) sizes of D2 saccades evoked by paired stimulation are plotted against horizontal and vertical initial positions of saccades, respectively. Data shown in B are used for this plot (S1 from central fixation point is also included). Coefficients of \(-0.72\) and \(-0.80\) mean that saccades are converging. E: scatter plots of regression coefficients calculated from horizontal versus vertical components of saccades. \( ● \) and \( ○ \) represent values obtained from D2 saccades and from S1 saccades (at different stimulation sites), respectively. Data evoked from 28 sites in FEF are included.

The saccade endpoint generally fell close to that of S1. The constancy of the endpoint of D2 with delays of 90–150 ms indicates that the endpoint was not much influenced with the stimulation delay. When the interval was as short as 30 ms, the endpoints slightly deviated from the S1 and the D2 amplitudes were smaller. This was because D2 often started before the end of D1 and the two saccades collided. If the interval was >200 ms, monkeys at times made voluntary return saccades starting from the endpoint of D1 to the fixation point, before the onset of D2. In that case, D2 was elicited during the course of the ongoing return saccade. Even in those special cases, D2 was directed toward the endpoint of S1, although the amplitudes of D2 were smaller.

Initially, we kept the fixation point illuminated while the...
When the eyes were deviated from a fixation point as a result of the first stimulation to the contralateral FEF, the saccades evoked with the second of the paired stimulation to the FEF (D2) were directed toward the endpoint of single saccades (S1) evoked from the same stimulation site. Under this condition, the second of the two-step saccade (D2) was by no means constant vector, but the direction and amplitude of the D2 was altered as if to compensate for the displacement caused by the first saccade (D1). The observation that the second of the paired saccade compensated for the first is not new (e.g., Guthrie et al. 1983; Sparks and Mays 1983; Sparks and Porter 1983; cf. Goldberg and Bruce 1990). In the present study, we utilized a new version of the paired-saccade technique to propose a new hypothesis on the functional organization of the FEF. There is some resemblance between the present findings and previous observations by Schlag and his colleagues (Dassonville et al. 1992; Schlag and Schlag-Rey 1990). They stimulated the FEF immediately after onsets of naturally occurring voluntary saccades and found that the evoked saccades (colliding on the ongoing saccades) compensated for the displacement during the initial part of the voluntary saccades. Our findings, however, differs crucially from theirs with respect to the following aspect. In Schlag’s colliding experiments, the timing between the occurrence of natural saccades and the stimulation of the FEF critically determined the amount of compensatory alterations of the saccade trajectories. Whereas the saccades evoked with the stimulation delivered shortly after (0–30 ms) the onset of voluntary saccades compensated for most of the intervening eye displacement, the compensation decayed greatly with longer intervals. In contrast, in our case, the endpoint of the second saccades (D2) was not much time-variant, remaining close to the endpoint of S1 with the stimulation interval of 60–250 ms. This time invariance in the saccade vector of D2 is important in interpreting our data with reference to a recent report. Nichols and Sparks (1995) stimulated the superior colliculus immediately after onsets of visually guided saccades. They found that the effect of preceding saccades on amplitudes of electrically evoked saccades decayed with a time constant of 45 ms. They interpreted their data as indicating that the time constant of the decay is determined by the time constant of the displacement integrator in the brain stem. In view of the nondecaying properties over the range of 60–250 ms in the present findings, the displacement integrator in the brain stem mechanisms can not account for the present observations of the long-lasting vector appearances of D2 saccades directed to the endpoint of S1. We should add that our present data in no way contradict the previous results because our approach of using a paired stimulation is different from previous studies employing voluntary saccades to which the electrical stimulation collided.

As an alternative explanation, we propose that the D2 vector reflects an aspect of functional properties of the FEF that has not been revealed. We interpret the fact that D2 saccades initiated from different eye positions always converge on the endpoint of S1 (Fig. 2C) as indicating that the FEF evokes saccades whose endpoint is determined on the basis of the fixation point. We now propose a hypothesis that vectors of saccades evoked from the FEF is calculated with reference to a point of interest for subjects. In the
present study, a point of interest seemed to be internalized as an internal reference point momentarily because the elimination of fixation targets at the time of stimulation delivery did not influence the saccade endpoint. By an approach of paired stimulation of the FEF, we introduced a condition where the eye positions at the time of FEF activation were dissociated from the fixation point (because of the deviation of eyes by a preceding D1 at the occurrence of D2). Thus, the D2 saccades appeared to converge on a single point calculated with reference to the fixation point. In most of previous studies, on the other hand, because the eye position at the time of FEF stimulation resided on internal reference points in the visual field, the saccades appeared as if it were fixed vector. In other words, the vector hypothesis as to the principal organization of the FEF output structures is valid as long as the current eye positions are not in conflict with internal reference points. Goldberg and Bruce analyzed a role of the FEF in directing double-step saccades (Hallett and Lightstone 1976) and proposed a model in which the dimensions of the second saccade are obtained by vector subtraction of the dimensions of the first saccade from the vector described by the retinal location of the target (Goldberg and Bruce 1990). This is valid in situations where voluntary saccades shifts the internal reference point from the fixation point (in the fovea) to individual saccade targets. In contrast, in the present study, we introduced a case where the internal reference point is not updated but remains at a certain point (fixation point in this study) by replacing voluntary saccades with electrical stimulation. In this case, the internal reference point seems crucial in calculating the second saccade of the double-step saccade. We suggest that, even in relation to voluntary saccades, an internal reference point may not necessarily be updated from a fixation point to a saccade target. We now propose to extend the model by Goldberg and Bruce and hypothesize that the FEF provides output signals for saccades to a visual target situated at a certain location in the visual field described with reference to the fixation point. It is important to add that our data do not support a notion that the FEF produces goal-directed saccades. We also add that the brain stem saccade generator, receiving outputs from the FEF, may perform the vector calculation based on the internal reference point (Moschovakis 1996).

Recent reports have suggested that the FEF is involved in cognitive aspects of oculomotor behavior, aside from its role in saccade generation (Bichot et al. 1996; Burman and Segraves 1994; Thompson et al. 1996). The present findings are in line with these studies and suggest that the FEF is able to utilize more flexible coordinate systems for saccade generation than the fixed-vector hypothesis predicts. Further studies are necessary to see how neural elements in the FEF would behave in association with a variety of cognitive oculomotor tasks.

We thank M. Kurama and Y. Takahashi for technical assistance. This work was supported by grants from Precursory Research Organization for Embryonic Science and Technology and the Ministry of Education, Science and Culture of Japan (08279101, 08044236, 06045470, 09680809). Address for reprint requests: J. Tanji, Dept. of Physiology, Tohoku University School of Medicine, Sendai 981, Japan.

Received 18 August 1997; accepted in final form 3 December 1997.

REFERENCES


