Spatial Processing in the Monkey Frontal Eye Field. I. Predictive Visual Responses

MARC M. UMENO[1,3] AND MICHAEL E. GOLDBERG[1,2]

[1]Laboratory of Sensorimotor Research, National Eye Institute, Bethesda, Maryland 20892; [2]Department of Neurology, Georgetown University School of Medicine, Washington, DC 20007; and [3]Department of Physics, The American University, Washington, DC 20016

Umeno, M. M. and Goldberg, M. E. Spatial processing in the monkey frontal eye field. I. Predictive visual responses. *J. Neurophysiol.* 78: 1373–1383, 1997. Neurons in the lateral intraparietal area and intermediate layers of the superior colliculus show predictive visual responses. They respond before an impending saccade to a stimulus that will be brought into their receptive field by that saccade. In these experiments we sought to establish whether the monkey frontal eye field had a similar predictive response. We recorded from 100 presaccadic frontal eye field neurons (32 visual cells, 48 visuomovement cells, and 20 movement cells) with the use of the classification criteria of Bruce and Goldberg. We studied each cell in a continuous stimulus task, where the monkey made a saccade that brought a recently appearing stimulus into its receptive field. The latency of response in the continuous stimulus task varied from 52 ms before the saccade to 272 ms after the saccade. We classified cells as having predictive visual responses if their latency in the continuous stimulus task was less than the latency of their visual ON response to a stimulus in their receptive or movement field as described in a visual fixation task. Thirty-four percent (11 of 32) of the visual cells, 31% (15 of 48) of the visuomovement cells, and no (0 of 20) movement cells showed a predictive visual response. The cells with predictive responses never responded to the stimulus when the monkey did not make the saccade that would bring that stimulus into the receptive field, and never discharged in association with that saccade unless it brought a stimulus into the receptive field. The response in the continuous stimulus task was almost always weaker than the visual ON response to a stimulus flashed in the receptive field. Because cells with visual responses but not cells with movement activity alone showed the effect, we conclude that the predictive visual response is a property of the visual processing in the frontal eye field, i.e., a response to the stimulus in the future receptive field. It is not dependent on the actual planning or execution of a saccade to that stimulus. We suggest that the predictive visual mechanism is one in which the brain dynamically calculates the spatial location of objects in terms of desired displacement. This enables the oculomotor system to perform in a spatially accurate manner when there is a dissonance between the retinal location of a target and the saccade necessary to acquire that target. This mechanism does not require an explicit calculation of target position in some supraretinal coordinate system.

INTRODUCTION

Early models of the saccadic system suggested that the brain took the retinal location of the target and used it to generate a goal toward which the eyes were driven (Westheimer 1989). The classical psychophysical experiments of Hallett and Lightstone (1976) showed that the saccadic system had access to a visual representation that was not obligately linked to the retina. Humans could make saccades to briefly flashed targets that, by virtue of an intervening saccade, had to be acquired by a saccade whose trajectory was not predicted by the retinal location of the target alone. This finding was replicated in the monkey by Mays and Sparks (1980). They used a double-step task in which the monkey was required to make successive saccades to two briefly flashed stimuli, both of which appeared and disappeared before the first saccade. They showed that neurons in the superior colliculus discharged before the second saccade when that saccade lay in their movement fields. In particular, a class of neurons with visual and premovement responses, the quasivisual cells, discharged long before the second saccade in a double-step task, at a time at which the target was not in the receptive field of the neuron. This experiment provided the first neurophysiological evidence that the saccadic system had access to a representation of the target in other than a retinal representation, and the authors postulated that this was a representation of target position in space occurring outside the superior colliculus and that projecting to the colliculus.

The frontal eye field also has neurons that discharge before visually guided saccades (Bruce and Goldberg 1985). There are three classes of these neurons: visual neurons that discharge in response to visual stimuli but not before purposive saccades made in total darkness; movement neurons, which do not have visual responses but do discharge before purposive saccades; and visuomovement cells that have both movement and visual activity. Goldberg and Bruce (1990) recorded from neurons in the monkey frontal eye field in the double-step task. They found that visual neurons discharged before the second saccade in the double-step task when the spatial location of the second target lay in the receptive field of the neuron after the first saccade. This activity occurred despite the fact that the stimuli never appeared in the receptive field of those neurons as determined by visual responses in a fixation task. Goldberg and Bruce postulated that this activity represented a transient change in the neuron's receptive field, and that calculation of this activity did not require an explicit representation of target position in a supraretinal space.

Goldberg et al. (1990) and Barash et al. (1991) made a similar observation on visual neurons in the monkey lateral intraparietal area (LIP). Duhamel et al. (1992a) subsequently demonstrated that neurons in LIP responded to stimuli that would be brought into their receptive fields by an

impending saccade even before that saccade occurred. This predictive response occurred even when the monkey never made a saccade to the stimulus that drove the neuron. Duhamel et al. suggested that this activity represented a transient shift of receptive field at the time of a saccade, so that the parietal cortex could process information in the coordinate system of the next fixation, and that this would obviate the need for either an explicit representation of target position in space or a time delay while the visual representation reestablished itself after the saccade. Walker et al. (1995) found similar predictive visual responses in the intermediate layers of the monkey superior colliculus.

In the present experiments we asked whether the monkey frontal eye field also had predictive visual responses. We were interested in this for two reasons. The first was to see whether the frontal eye field had predictive visual responses associated with a single saccade, as well as those demonstrated in the double-step task. The second was that predictive visual responses had been previously demonstrated only in areas in which there is no clear distinction between visual and movement cells. The predictive response could represent motor planning for a saccade that never occurred. However, in the frontal eye field, if the activity occurred on the visually responsive cells and not on the movement cells, then at least here the predictive response could be dissociated from a movement signal. In these experiments we show that predictive visual responses are found in visual and visuomovement neurons but not in movement neurons. A preliminary report of these experiments has been presented elsewhere (Umeno and Goldberg 1994).

METHODS

Two adult male rhesus monkeys (*Macaca mulatta*) served as subjects in this experiment. The monkeys were trained to perform oculomotor tasks during neurophysiological recording (Wurtz 1969). In preparation for these experiments, the monkeys were first taught to fixate a visual target to receive a liquid reward. They were then trained on the tasks that were to be performed in this experiment. This training period lasted a few days. One of the monkeys had been trained extensively on similar tasks and one of the monkeys had no prior training. There were no apparent differences in the behavior of these monkeys. We prepared the monkeys for chronic neurophysiological recording with the use of sterile surgical technique under ketamine-induced isoflurane general anesthesia. Each monkey was implanted with recording chambers over the areas of interest, a head holder to restrain the head during physiological recording, and scleral search coils (Judge et al. 1980; Robinson 1963) to monitor eye position. The animals were allowed to recover for ≥1 wk from the surgery before any experiments were performed. The animals' weight, fluid intake, and general health status were carefully monitored. Periodic removal of granulation tissue on the dura was necessary. This involved anesthetizing the monkeys with ketamine and surgically debriding the surface under a dissecting microscope. All procedures were approved by the Animal Care and Use Committee of the National Eye Institute in compliance with the Public Health Service Guide for the Care and Use of Laboratory Animals.

Physiological methods

Monkeys were housed singly or in pairs in an unrestrained manner between recording sessions. During the recording sessions the monkey sat comfortably in a polycarbonate primate chair. The monkey's head was restrained with the use of a metal post affixed to the implanted head holder. The head holder then was placed into a metal sleeve joining it to another post attached to the chair. The monkey faced a tangent screen 57 cm away, watching visual stimuli consisting of red light-emitting diodes (LEDs) back-projected onto the screen (intensity 0.4–1.5 cd/m^2). The room was nearly dark, illuminated only by background light from the recording instruments. Neurons were sampled with the use of a tungsten electrode driven by a hydraulic microdrive system. The electrode was positioned regularly through a stainless steel guide tube with the use of a plastic grid (Crist et al. 1988). The guide tube was first lowered without the electrode, and then the electrode was placed into the brain manually and affixed to the microdrive, which was controlled manually with a hydraulic system (Narashige). A Hewlett-Packard HP Vectra 486/337 machine controlled the experiment with the use of the REX (Real Time Experimental) control language (Hays et al. 1982). This software, running under a real-time (QNX) operating system, allowed both computer control over the experimental hardware and the collection of data at a sample rate of 1 kHz per channel. The microelectrode signals were low-pass filtered at 8 khz with the use of an active Butterworth filter, and analyzed on-line with the use of a computer implementation of the Abeles-Goldstein principal component algorithm running on a Dell System 310 386 (Gawne and Richmond 1993). Each isolated neuronal action potential resulted in a digital pulse sampled by the REX computer at 1 kHz.

Behavioral paradigms

A variety of experimental paradigms was used to control the oculomotor behavior of the monkey and present relevant and irrelevant stimuli.

DELAYED SACCADE TASK. The monkey was required to hold the gaze on a fixation point (FP, Fig. 1A), a dim red spot 1/2° diam back-projected on the tangent screen by an LED. At this time the receptive field of the neuron under study was at a certain location on the tangent screen that we call the current receptive field (CRF). During this fixation, a peripheral visual stimulus STIM (a 2nd red LED 1° diam) appeared in the CRF and then was extinguished after a brief interval, usually 300 ms. When the FP disappeared, the monkey made a saccade to the location of STIM, even though the target was no longer visible. The light at STIM reappeared after the saccade and the monkey was rewarded for holding fixation at that location for 100 ms (Hikosaka and Wurtz 1983a). With this paradigm both a visual response to the appearance of the stimulus and a movement discharge to the subsequent saccade could be observed in a single task. This task was used to classify the cells as visual, visuomovement, or movement. Visual cells responded in a time-locked manner to the onset of the STIM light in their receptive fields and were silent during the saccade. Movement cells were silent during the STIM presentation and discharged just before saccades to their movement fields. Visuomovement cells both responded to the visual stimulus and also discharged before the saccade (Bruce and Goldberg 1985). The STIM and FP images were controlled by General Scanning servo-controlled mirror galvanometers that were under the control of signals generated by D/A converters in the computer. The General Scanning devices could move the images 20° in 8 ms, and the LED was extinguished while the mirror moved to avoid streaking of the image on the retina. The stimulus locations could be controlled by joystick or read out from a table of values. By moving the STIM position we could ascertain the receptive and movement fields of the neurons. We defined the receptive field eccentricity as the eccentricity of the location that gave the highest frequency discharge as estimated by on-line rasters.
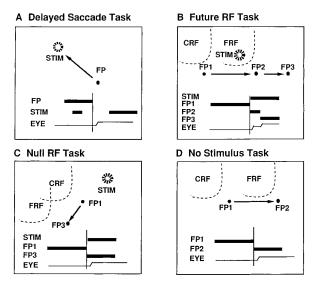
FIG. 1. Oculomotor tasks used in this experiment. In this and subsequent figures, each box represents visual environment and timing diagrams for experiment. Locations of light-emitting diode (LED) fixation points (FPs) and stimuli are denoted in diagrams. FP: initial FP for task. Arrow: saccade that was to be executed sometime during experiment. Dashed curves: position of current receptive field (CRF) or future receptive field (FRF) of neuron being examined. Dashed circles: visual stimuli (STIM). Bars at *bottom of boxes*: timing diagrams for tasks. If bar is present, then corresponding visual feature is activated. Each line at *bottom of boxes* represents 1-dimensional position trace of eye. In this figure, theoretical horizontal eye traces are shown (EYE). Vertical line: time at which monkey was asked to begin saccade. *A*: delayed saccade task. For this task, monkey was required to hold fixation at spatial location of FP until FP was extinguished. During this fixation, visual stimulus appeared at location of STIM and subsequently was extinguished after fixed period of time. As FP was turned off, monkey was required to make saccade with no visual target to remembered spatial location of STIM. To reinforce behavior, STIM reappeared some fixed time after saccade was executed. *B*: FRF task. monkey had to make saccade from FP1 to FP2 after FP1 was extinguished and both FP2 and STIM appeared. Saccade to FP2 brought location of STIM from cell's FRF into its CRF. After short fixation period, monkey had to make saccade from FP2 to FP3, which was not location of STIM, rendering STIM behaviorally irrelevant for this task. *C*: null receptive field task. Monkey made saccade from FP1 to FP3, which was not same saccade as in previous tasks. This saccade kept STIM outside receptive field of neuron. *D*: no stimulus task. Monkey made same saccade from FP1 to FP2 as in predictive task, except in this task STIM was not present.

CONTINUOUS STIMULUS TASKS. We determined the stimulus location that gave the most intense discharge as estimated by an on-line raster calculation, and then used that location as the receptive field stimulus in future experiments. In addition, we ascertained a number of stimulus locations that gave no response in the delayed saccade task, and used those locations as other saccade target and visual stimulus locations. In the continuous stimulus tasks we asked the monkey to make a saccade that moved an extraneous stimulus from one retinal location to another (Fig. 1, B and C). The monkey fixated FP1, then simultaneously, while the fixation light was extinguished, a jump target (FP2) and visual stimulus (STIM) appeared outside the CRF of the neuron being studied. The monkey was required to make a priming saccade to FP2, ignoring STIM. This priming saccade moved the neuron's receptive field to a new spatial location that we call the future receptive field (FRF). The jump target was the same LED as the FP, and the STIM target was larger. Early in training the monkeys occasionally made saccades to the STIM target. However, because the stimuli were different and the trial was aborted if the monkey made a saccade to STIM instead of to FP2, the monkeys rapidly learned which was the correct saccade target, and during most recording sessions never

made a saccade to the STIM target. Depending on the direction of the priming saccade, STIM could be in the FRF (FRF task, Fig. 1*B*) or it could be outside both the CRF and FRF (null receptive field task, Fig. 1*C*). In the FRF task, the priming saccade moved the retina so that STIM was then positioned in the CRF. In the null receptive field task the saccade moved the retina so that STIM was still not positioned in the CRF. After the priming saccade was completed, some hundreds of milliseconds later, a second saccade from FP2 to FP3 was made to eliminate the possibility that the monkey would make a subsequent saccade to STIM. The saccade from FP2 to FP3 was always outside the movement field of the cell, and FP3 was never in an FRF or CRF. Note that STIM never served as a saccade target for the monkey, and was behaviorally irrelevant (Walker et al. 1995).
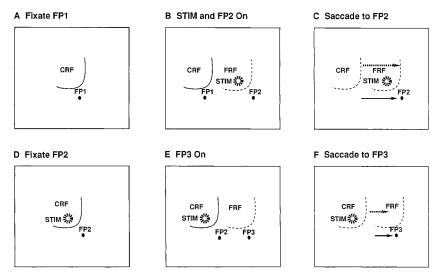
NO STIMULUS TASK. The monkey fixated a central FP (FP1, Fig. 1*D*), then made a visually guided saccade to an LED target (FP2) when FP1 was extinguished. Usually the saccade from FP1 to FP2 was identical to the priming saccade in the continuous stimulus task, the only difference being that STIM was not present. Thus this task could be used as a control task by reproducing the saccade made in the continuous stimulus task without the presence of a visual stimulus. The tasks were either run in blocks of a single task or with the four different tasks randomly interleaved.

Description of experimental events

The timing of the events in the continuous stimulus task is critical to these experiments. Figure 2 details the events as they would have taken place during a typical experiment with the use of the FRF continuous stimulus task. Initially, the monkey fixates FP1 and thus there is a CRF associated with it (Fig. 2*A*). After a short fixation period, simultaneously, a saccade target at FP2 and a behaviorally irrelevant STIM appear (Fig. 2*B*). Because the monkey will soon acquire a new FP, there is an FRF associated with the impending eye movement. The old FP is subsequently extinguished and the monkey makes a saccade to FP2 (Fig. 2*C*). As the monkey reaches FP2, the CRF for the neuron has been shifted to what was previously the FRF (Fig. 2*D*). The exact instant at which STIM enters the CRF depends on the relationship of STIM to the receptive field and the dynamics of the individual saccade. Because of this ambiguity we use the stringent assumptions that we are only sure STIM is in the FRF before the saccade, and we are only sure that it is in the CRF after the saccade. Another saccade target FP3 appears briefly after the monkey reaches FP2 (Fig. 2*E*), assuring that STIM is not behaviorally significant because the monkey does not get rewarded for paying attention to it in any way. Finally, FP2 is extinguished as FP3 is turned on and the monkey makes a saccade to FP3, away from STIM (Fig. 2*F*). At this time STIM may or may not be in the new CRF, depending on the size of the receptive field. Because frontal eye field cells frequently have poorly determined outer bounds (Bruce and Goldberg 1985), it is often difficult to find a location for FP3 that brings the CRF entirely off of STIM. However, FP3 is always positioned to be well out of the CRF when the monkey is fixating FP2.

Data analysis

We determined each neuron's visual latencies and discharge frequency off-line with the use of a series of data analysis programs running on a Silicon Graphics workstation. We rejected trials in which the monkey failed to earn a reward. We digitally differentiated eye position traces with the use of a finite impulse response filter, and used the resulting velocity trace to determine the beginning and end of saccades by computing when the velocity rose above and returned to the background level, respectively. We verified the computer's estimate of saccade beginning and end by visual inspection of the traces. Rasters, histograms, and cumulative

FIG. 2. Description of events in continuous stimulus FRF task. Events of task are separated into each box. Solid curves: location of receptive field of hypothetical neuron being examined. A: monkey fixates FP1; neuron's CRF is located at CRF. B: saccade target FP2 and visual stimulus STIM appear. Because monkey is going to make saccade to FP2, neuron now has FRF (- - -) associated with saccade. C: monkey makes saccade to FP2 (solid arrow: saccade). During this period receptive field of neuron is moving from CRF to FRF (dashed arrow: shifting receptive field). D: monkey acquires FP2 and now neuron has new CRF with STIM placed in it, which should cause neuron to fire. E: another saccade target FP3 appears, which means there is new FRF associated with saccade. This target is not in direction of STIM, thus rendering STIM behaviorally irrelevant. Monkey does not have to attend to STIM in any way to receive reward. F: monkey makes saccade to FP3, away from STIM, which once again moves receptive field of neuron. Monkey will then fixate FP3 to receive reward.

histograms synchronized on stimulus onsets and disappearances and saccade beginnings and ends were calculated from the accepted trials with the use of a binwidth of 2 ms. The cumulative histogram was differentiated and, to determine the beginning of a given burst, a cursor was placed at the first significant change in this curve following the appearance of the stimulus or the signal to make the saccade. Cursor placement was verified by inspection. Spike discharge frequency was calculated as the average spike count in the 100 ms following the onset of the burst. To calculate discharge latency we displayed a cumulative histogram on a computer monitor with a cursor placed to the left of the inflection point of the cumulative histogram as estimated by the computer and verified by the investigator. The cursor was positioned before the earliest increase of discharge in any of the trials as estimated from the spike raster. The time of occurrence of the first spike after this cursor was considered to be the latency of the response for each trial. The latencies from each trial were averaged. Because the latency from saccade onset and not the latency from the end of the saccade was measured, we avoided the difficulty of determining at what point during the saccade the stimulus would have crossed into the receptive field. If the difference between the latency from saccade onset and the visual ON response latency was negative, we considered the neuron to have a predictive visual response. Student's *t*-tests were used to see whether the latency of the ON response in the delayed saccade task was significantly different from the latency of the reafferent response when the stimulus entered the receptive field by virtue of the saccade.

Histological methods

The first monkey was deeply anesthetized with pentobarbital sodium and perfused first with normal saline and then with 10% Formalin in normal saline. The monkey was then prepared with the use of standard techniques (Ma et al. 1991) for histological examination of the frontal eye field. The electrode tracks were found in the frontal eye field in the expected area from the surface predicted by the electrode penetration records. The second monkey is still being used for other experiments. Because of the well-known unique physiological characteristics of the frontal eye field and our long experience with that structure (Bruce and Goldberg 1985; Goldberg and Bushnell 1981; Mohler et al. 1973; Segraves and Goldberg 1987), we decided that it was not necessary to delay this report until we had located the electrode tracks.

RESULTS

We recorded from 100 frontal eye field presaccadic cells in three hemispheres of two awake behaving rhesus mon-

keys. The delayed saccade task was used to determine the cell type of each presaccadic neuron that was examined. The criteria used for this classification were the same as those used by Bruce and Goldberg (1985). The visual cells responded to the onset of the visual stimulus, but had no activity related to the saccade. Visuomovement cells discharged both in response to the onset of the stimulus and before the onset of the saccade. Movement cells discharged only to the onset of the saccade and not to the onset of the stimulus. We identified 32 visual cells, 48 visuomovement cells, and 20 movement cells. We then tested each of the 100 frontal eye field cells with the use of the FRF task. All of the visually responsive neurons, both visual and visuomovement (80 of 100), had a significant response to a visual stimulus that appeared in the FRF of the cell and was brought into the CRF by the saccade. None of the movement cells had any response in this task.

Visual cells

It is not surprising that a visually responsive neuron responds to a stimulus brought into its receptive field by a saccade. Neurons would be expected to have such a reafferent response. Because the real world is remarkably devoid of flashing lights, most visually responsive neurons are stimulated by such reafferent events most of the time. However, 31% (25 of 80) of the visually responsive cells in this study responded to a stimulus in the FRF with a latency that could not be explained simply as a reafferent response. This response occurred frequently before the saccade began. We describe such responses as predictive visual responses. A visual neuron that demonstrated a predictive visual response is shown in Fig. 3. In the delayed saccade task the cell responded phasically to the appearance of the stimulus with a latency of 78 ms (Fig. 3A, *left*). It did not discharge before the movement, as can be seen in the activity of the cell in the same trials synchronized on the saccade beginning (Fig. 3A, *right*). In the FRF task (Fig. 3B), the cell began to discharge at or just before the beginning of the saccade. The activity was not a motor or postsaccadic discharge related to the movement. When the monkey made the saccade in the absence of the

A Delayed Saccade Task

B Future Receptive Field Task

Stimulus Appearance   Saccade Beginning

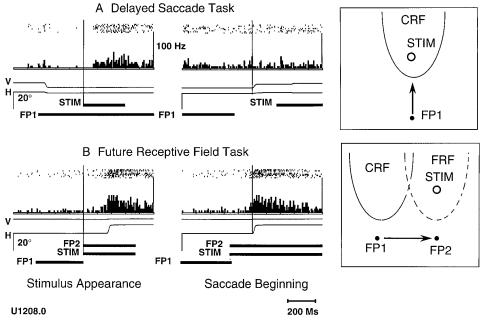U1208.0   200 Ms

FIG. 3. Responses of predictive visual cell. For this and subsequent figures, response rasters and histograms are depicted. In raster diagram each dot represents neuronal discharge. Successive trials are synchronized on trigger event that occurs at vertical line. Only data from trials in which monkey received reward are included. Histogram sums trials in raster. Vertical calibration line on *bottom right* of each raster diagram: discharge rate of 100 Hz. This level varies among subsequent diagrams because number of trials in each diagram is different. If there are 2 raster diagrams present, they represent same neuronal responses aligned on different events. *Left raster diagram* is always aligned on stimulus onset and *right raster diagram* is always aligned on saccade beginning. Drawing on *right*: physical relationships of stimuli. Actual example of eye movements (H, horizontal; V, vertical) and stimulus timing from 1 of the trials depicted in rasters beneath each raster, with events synchronized to raster. Twenty-degree eye calibration line is at *left* of eye traces. Delayed saccade task (*A*): cell responded when stimulus STIM appeared in its receptive field (*right*). Cell did not discharge before or during saccade to location of extinguished STIM (*left*). FRF task (*B*): monkey made rightward saccade that brought STIM into its receptive field. Cell discharged before saccade onset in continuous stimulus predictive task.

stimulus (no stimulus control, Fig. 4*A*), the neuron did not discharge. The activity was not a direct visual or attentional response to the stimulus for two reasons. First, the

latency to the appearance of the stimulus in the FRF was well over 200 ms, as opposed to the 78-ms latency of the visual response to the stimulus in the CRF. Second, the
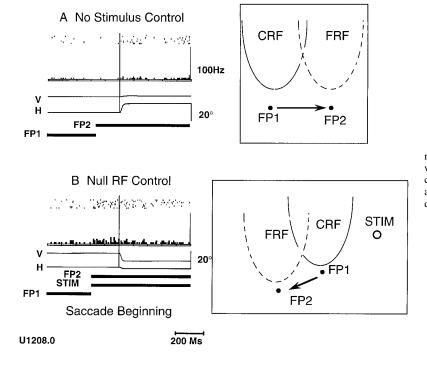
A No Stimulus Control

B Null RF Control

Saccade Beginning

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FIG. 4. No stimulus control (*A*): monkey made same rightward saccade from FP1 to FP2 as in Fig. 3*B*, but there was no stimulus in FRF. Cell had very little response. Null RF control (*B*): monkey made saccade that brought same stimulus as in Fig. 3*B* to retinal location still not in RF. Cell does not discharge.
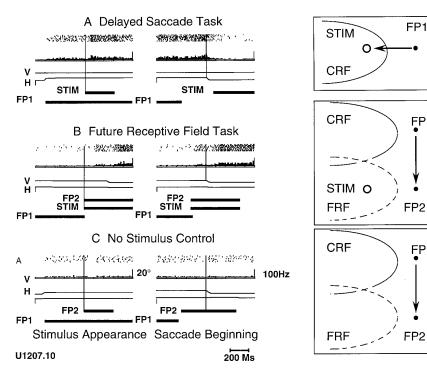
A Delayed Saccade Task

B Future Receptive Field Task

C No Stimulus Control

Stimulus Appearance　Saccade Beginning

U1207.10

200 Ms

FIG. 5. Responses of predictive visuomovement cell. Delayed saccade task (*A*): cell has both visual response to stimulus (*left*) and movement response (*right*) to that same location in delayed saccade task. FRF task (*B*): monkey made downward saccade that brought STIM positioned into its receptive field. Cell fired well before saccade began, much earlier than time when stimulus was moved into its receptive field. Cell discharged ~100 ms after stimulus presentation. No stimulus control task (*C*): cell did not discharge when monkey made same saccade as in above FRF task, 20° downward from FP1 to FP2, without presence of STIM in its receptive field.

cell did not burst when the monkey made a saccade that did not move the stimulus into the receptive field, but instead moved it from one retinal location outside the receptive field to another retinal location outside the receptive field (Fig. 4*B*). The activity was clearly dependent on the monkey making a saccade that brought the stimulus into the receptive field. It must have been a visual response to a stimulus in the FRF. We defined this activity as a predictive visual response (Walker et al. 1995). Of the visual cells examined, 31% (10 of 32) had predictive visual responses. A slight change in background activity, without a burst, can be seen around the saccade in Fig. 4*A*. We occasionally saw such background changes after a series of continuous stimulus trials, and we are preparing a separate report on this effect.

Visuomovement cells

We found predictive visual responses in 31% (15 of 48) of the visuomovement cells, a typical example of which is shown in Fig. 5. Figure 5*A* shows that the cell had both a visual response to the stimulus onset and a movement response to the saccade onset during the delayed saccade task. The cell responded 68 ms after stimulus presentation, continued to discharge during the delay period, and also slightly increased its discharge before the saccade. If we asked the monkey to perform the FRF task, making a saccade from FP1 to FP2 that brought STIM into its receptive field (Fig. 5*B*), the cell discharged time-locked to the beginning of the saccade onset even though the visual stimulus was not yet in its receptive field as determined in the delayed saccade task. The latency of this response was 83.3 ms before the saccade (Fig. 5*B*, *right*). The latency of cell discharge to the stimulus onset was >100 ms in the continuous stimulus task, as compared with the 68-ms latency of the visual response in the delayed saccade task.

Movement cells

We studied 20 movement neurons in the FRF task. No cell had any response either before or after the saccade during that task (Fig. 6). The cell shown had a movement response around 40 ms before the saccade onset and no response to the stimulus onset during the delayed saccade task (Fig. 6*A*). When the monkey performed the FRF task (Fig. 6*B*), there was no response from the cell.

Sample characteristics

For each of the visually responsive neurons, the latency of the visual ON response during the continuous stimulus task was measured and then compared with the latencies of responses from the FRF task (Fig. 7). The visual ON response latencies from stimulus onset in the delayed saccade task ranged from 62 to 114 ms. The distribution of latencies from saccade onset in the FRF task was continuous, ranging from −84 to 272 ms from the beginning of the saccade. Thus there were no separate groups distinguishable on the basis of latencies from saccade onset for the FRF task in this population of frontal eye field neurons.

To classify the cells as predictive or not predictive, we subtracted the latency of the visual ON response from the latency from saccade onset (Fig. 8). We called this measure the adjusted latency. If a cell had a statistically significant negative adjusted latency ($P < 0.0002$ by Student's *t*-test), we classified it as predictive because its activity could not have been explained by the eye movement's bringing the stimulus onto a retinal receptive field; otherwise we classified it as not predictive. Thirty-one percent (10 of 32) of the visual cells and 31% (15 of 48) of the visuomovement cells were predictive. There was a continuous distribution of differences in latencies and the predictive visual responses
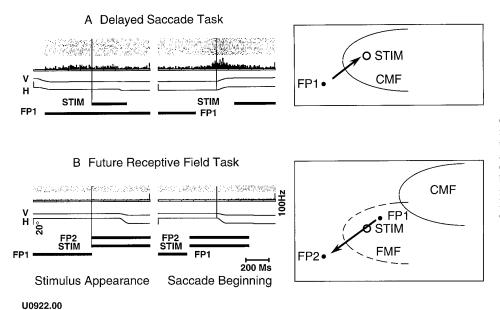
A Delayed Saccade Task

B Future Receptive Field Task

Stimulus Appearance   Saccade Beginning

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FIG. 6. Activity of typical movement cell. Delayed saccade task (*A*): cell had movement response before saccade from FP to location of STIM and had no response to appearance of STIM in that same location. Current movement field (CMF) is outlined by solid line. FRF task (*B*): cell remained inactive at saccade onset during FRF task. Future movement field (FMF) is outlined by dotted line.

occurred in a continuous distribution of latencies for the frontal eye field cells.

We also compared the magnitude of the neuronal responses during the continuous stimulus FRF task with the visual ON responses during the delayed saccade task (Fig. 9). It is clear that the responses in the continuous stimulus task were lower than the visual ON responses during the delayed saccade task, because the great majority of the cells fell below the $X = Y$ line in this plot. The average discharge in the FRF task was 0.73 ± 0.29 (SD) of that of the visual ON response for nonpredictive cells and 0.71 ± 0.38 (SD) for predictive cells. The difference was not statistically significant ($P > 0.9$) with Student's *t*-test.

Most of the cells that we studied had receptive fields whose inner margins were ≤25° from the fovea. All of the

cells with predictive responses were in this range. We studied eight cells with more eccentric receptive fields, but none of them had predictive responses. Figure 10 compares receptive field eccentricity with adjusted latency in the continuous stimulus task. If a receptive field were located >25° from the FP, the adjusted latency was >0.

DISCUSSION

In these experiments we demonstrate that the monkey frontal eye field has a predictive visual mechanism, like the LIP (Duhamel et al. 1992a,b) and the intermediate layers of the superior colliculus (Walker et al. 1995). Neurons respond to stimuli that will be brought into their visual receptive fields by saccades, sometimes even before those saccades actually take place. They would not respond to those stimuli in a fixation task, nor do they discharge in association
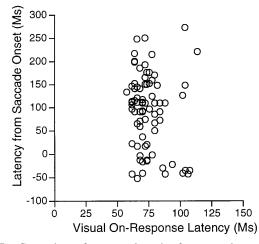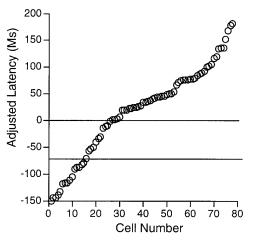

FIG. 7. Comparison of response latencies from saccade onset in predictive task vs. visual ON response latencies during delayed saccade task for all visually responsive cells. Each triangle represents latency of a single visual or visuomovement cell from saccade onset in predictive task plotted against visual latency of same cell in delayed saccade task. For predictive task, latencies were measured from beginning of saccade from FP1 to FP2. Latencies <0: discharge before saccade onset. Visual ON response latencies were measured in delayed saccade task after onset of STIM.

FIG. 8. Ordered plot of adjusted saccade latency (L_a), defined as latency before saccade in continuous stimulus task (L_s) minus latency of visual ON response (L_v) ($L_a = L_s - L_v$) plotted against ordinal cell number. All cells whose adjusted latency was <0 were predictive by Student's *t*-test. All cells whose adjusted latency was less than −70 ms reliably discharged before saccade began. Lines at 0 and −70 drawn for convenience.

with the saccade unless the saccade is going to bring the target into the receptive field. This mechanism enables the frontal eye field to identify potential saccade targets for a saccade that will take place after an intervening saccade. We discuss this phenomenon in relation to whether the predictive mechanism should be considered a property of visual or motor processing, in relation to the properties of other brain areas, and in relation to the problem of spatially accurate oculomotor behavior.

Predictive responses as a property of visual processing

The monkey frontal eye field has three classes of neurons that discharge before visually guided saccades: visual cells, which respond to visual stimuli but not before learned saccades made in total darkness; movement cells, which discharge before saccades but have little or no visual activity; and visuomovement cells that have both visual and movement activity (Bruce and Goldberg 1985). Although the visual and movement cells are distinct, the visuomovement cells form a continuum from relatively weak movement and strong visual discharges to strong movement and weak visual discharges. The movement cells and a few strongly movement-related visuomovement cells project to the superior colliculus (Segraves and Goldberg 1987) and pons (Segraves 1992).

In the two other populations of neurons in which the predictive response has been described, LIP and the intermediate layers of the superior colliculus, there is no such clear distinction between visual and movement neurons. All of the intermediate layer collicular neurons that show the response have both visual and movement responses, and most resemble the buildup neurons classified by Munoz and Wurtz (1995). Although the huge majority of the neurons in LIP has visual responses, many of these neurons also have movement responses (Colby et al. 1995), and LIP does not have a clear segregation of cell type like the frontal eye field. In addition, the original experiments describing the response were performed with the use of a single saccade that brought the stimulus into the receptive field. In those sets of experi-

FIG. 10. Comparison of receptive field eccentricities with adjusted latency. Absolute receptive field eccentricity was estimated with the use of delayed saccade task by finding placement of STIM that elicited strongest response from each cell.

ments one could argue that the predictive response was not a visual response; instead it could have been an attempt by the brain subsequently to drive the eyes to the target that evoked the response. This oculomotor command could be canceled elsewhere, at the level of the substantia nigra (Hikosaka and Wurtz 1983b) or even the pontine omnipause neurons (Hepp et al. 1989).

In the frontal eye field, however, it is clear that the predictive response is a function of visual processing, for two reasons. 1) the effect is seen in the visual cells and not in the movement cells. 2) the effect is seen even under conditions in which the monkey is required to make a subsequent saccade that goes away from the CRF at FP2. It is difficult to argue that the predictive effect depends on motor planning for an actual saccade when no sign of it can been seen on the cells that have the motor discharge, and when it occurs despite the fact that monkey makes a predictable subsequent saccade that is directed away from the receptive field. The only alternative interpretation is that the visual processing mechanism can use a corollary discharge from the motor system to compensate for the impending eye movement. Because the predictive response often precedes the saccade, the effect cannot arise from oculomotor proprioceptors.

The effect may require some level of behavioral modulatory control as well as purely visual processing. Burman and Segraves (1994) showed that visual neurons in the frontal eye field fail to discharge when a monkey makes a saccade that brings a stimulus into their receptive field, if that stimulus is a portion of a picture that the monkey has been exploring, unless the monkeys will actually make a saccade to the stimulus. In our experiments the reafferent response of the neuron is less intense than the visual ON response, which suggests that the visual response begins to wane even in a few hundred milliseconds, and that the determining factor of this response decrement is not time in the receptive field, but rather time in the entire visual field. Such a novelty-dependent response could be considered to have a modulatory component related to the behavioral significance of the stimulus that serves as a gain control on the visual input. However, it is clear that this novelty-related component is
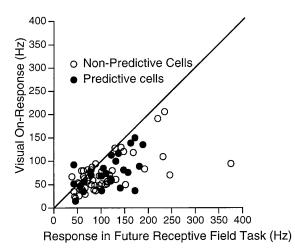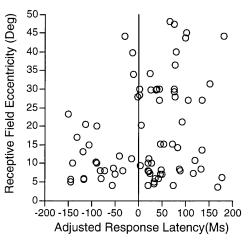

FIG. 9. Comparison of continuous stimulus task responses to stimulus in FRF with visual ON responses in delayed saccade task. Diagonal line: equal responses from both tasks ($X = Y$). Open circles: nonpredictive cells. Filled circles: predictive cells.

not specifically related to the generation of saccades, because it occurs whether or not a saccade to the stimulus is remotely probable.

Because the effect clearly has a modulatory component, we cannot exclude the possibility that the predictive response is an enhanced visual response to the stimulus occurring because of the saccade from FP1 to FP2. We think that this is unlikely for two reasons. *1*) The cell never responded to the appearance of the stimulus in the FRF, but enhancement of the visual response always occurs at the appearance of the stimulus and not necessarily at the time of the saccade (Goldberg and Bushnell 1981). *2*) Saccade-related enhancement of visual responses in the frontal eye field is spatially specific, occurring only when the saccade is made to a stimulus in the receptive field. We always chose the FP1 to FP2 saccade to be as far away from the center of the receptive field as possible given the geometry of the screen and field. Whenever possible, the saccade target and the FRF stimulus were ipsilateral to the hemisphere under study. Frontal eye field neurons are general contralateral in their receptive fields (Bruce and Goldberg 1985) and the saccades evoked by electrical microstimulation from their sites are inevitably contralateral and directed into the movement and receptive fields of the neurons (Bruce et al. 1985). Because the enhanced discharge is probably a part of the mechanism of target selection for saccades (Goldberg and Bushnell 1981; Schall and Hanes 1993; Wurtz and Mohler 1976), it is unlikely that such a target selection would enhance stimuli diametrically opposed from the saccade direction of the cell under study.

The predictive response that we demonstrate explains results in other studies of the frontal eye field. One of the visual neurons reported by Goldberg and Bruce (1990) (their Fig. 6) clearly discharges before the saccade that brings the spatial location of the flashed stimulus into the receptive field. This could easily be a predictive effect. Burman and Segraves (1994) report that frontal eye field visual neurons that discharge before visually guided saccades to stable stimuli in their receptive field frequently discharge before the saccade that brings the stimulus into the receptive field. This effect must be a predictive visual response.

Relationship to the LIP and the superior colliculus

Predictive visual responses have been described in LIP (Duhamel et al. 1992) and the intermediate layers of the superior colliculus (Walker et al. 1995). There are reciprocal projections from LIP to the frontal eye field (Barbas and Mesulam 1981; Stanton et al. 1995), and it is conceivable that visually responsive cells in LIP could relay the predictive signal to the frontal eye field, or that the frontal eye field could project its signal to LIP.

Some of the visuomovement cells in the intermediate layers of the superior colliculus also have a predictive response (Walker et al. 1995). This visual response is suppressed around the saccade, unlike that in the frontal eye field, where we found no saccadic suppression. Although the frontal eye field projects to the superior colliculus (Stanton et al. 1988), it is unlikely that the colliculus receives its predictive responses directly from the frontal eye field. The presaccadic neurons that project from the frontal eye field to the superior

colliculus are movement neurons or visuomovement neurons with very strong movement responses, and not the strongly visual neurons that contain the predictive responses in the frontal eye field (Segraves and Goldberg 1987). Presumably if the collicular predictive mechanism is not generated de novo in the superior colliculus it comes from LIP.

Maintenance of spatial accuracy by the oculomotor system

Although the cortical oculomotor system seems to be organized in terms of desired displacement of eye movement (Barash et al. 1991; Bruce and Goldberg 1985), it functions in a spatially accurate fashion (Hallett and Lightstone 1976). This has clearly been demonstrated by the study of neurons in the double-step task (Barash et al. 1991; Bruce and Goldberg 1985; Goldberg et al. 1990; Mays and Sparks 1980). In this task subjects are asked to make successive eye movements to two targets that appear briefly and sequentially before the first saccade begins. The retinal vector of the first target and the vector of the saccade necessary to acquire it are identical. However, the saccade necessary to acquire the second target cannot be calculated with the use of only the retinal position of the second target. This was originally taken to indicate that the oculomotor system had access to the absolute spatial position of the target. There is a noticeable paucity in the oculomotor system of signals describing the absolute position in space of a visual target. Zipser and Andersen (1988) pointed out that such a signal could be calculated from parietal retinotopic and eye position signals. Such a signal is present in the eye position signals of the extraocular motor neurons themselves (Robinson 1970). However, rather than arising from a distributed cortical network that calculates target position in space, the eye position signal on eye muscle nuclear neurons clearly arises from brain stem mechanisms in the medial vestibular nucleus and nucleus prepositus hypoglossi that integrate brain stem eye velocity signals (Cannon and Robinson 1987; Cheron et al. 1986). These velocity signals in turn must arise from collicular and frontal eye displacement signals that already reflect spatially accurate processing (Goldberg and Bruce 1990; Mays and Sparks 1980). These results suggest that, like LIP and the intermediate superior colliculus, the frontal eye field has access to a mechanism that shifts the visual representation into a coordinate system whose origin is the projected center of gaze following the impending saccade. This mechanism produces the required spatially accurate displacement signal.

Goldberg and Bruce (1990) pointed out that the calculation necessary to compute the second saccade in the double-step task can be described by the mathematical formalism of vector subtraction: the second saccade is the retinal vector of the second target minus the vector of the first saccade. A mechanism that relies on such a vector subtraction process would not necessitate an explicit calculation of target position in space. Recent clinical evidence suggests that the human brain uses such a vector subtraction system: certain patients with frontoparietal or parietal lesions cannot perform the double-step task when the first movement is directed contralateral to their lesion (Duhamel et al. 1992b; Heide et al. 1995). The patients then fail to make a saccade to a stimulus that appeared in the visual field and in the

saccade direction mediated by their intact cortex. Clearly, because under many circumstances patients can acquire that target, if the brain used a strategy of determining absolute spatial position the patients should have access to it. However, because they cannot compensate for certain directions of eye movements, it is possible that they are lacking the predictive response demonstrated in these experiments, and do not use an estimate of absolute position.

The predictive response forces a reinterpretation of the significance of the message transmitted by frontal eye field neurons. Kuffler (1953) described the receptive field of a retinal ganglion cell as that area of the retina that can evoke visual responses in the neuron. The tacit assumption ever since has been that receptive fields describe retinal location. The predictive phenomenon shows that this assumption is not true for the visual cells in the frontal eye field. Discharge in a neuron with a predictive response does not specify a retinal location. Instead, it specifies that a stimulus is in a spatial location a certain displacement from the current or impending center of gaze. This vector is equivalent to the vector of the next saccade that would be necessary to acquire the target. It is not dependent on the retinal location of the target. Although the retinal location of the receptive field moves, the output meaning of the cell is invariant. This invariance provides the spatial accuracy demanded by the oculomotor system. Whenever an impending saccade changes the spatial meaning of a retinal location, that spatial location excites a new population of frontal eye field neurons that ordinarily respond to a different retinal location. This predictive signal is reinforced after the saccade by visual signals from the new retinal location. The utility of the predictive response is that it allows processing before a saccade to occur as if the saccade had already taken place, and does not require the reestablishment of the visual representation by a set of new responses from the retinal locations to which the saccade has moved the targets.

A similar shifting receptive field mechanism has been described in the skeletomotor system. Graziano and Gross (1993) have demonstrated neurons in the monkey putamen whose receptive fields move with the limb but are independent of gaze angle (Graziano et al. 1994). Those researchers postulated that this activity locates visual targets in the coordinate system of the moving limb. The activity that we have demonstrated locates visual targets in the coordinate system of the moving eye.

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